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REVIEW ARTICLE

Plasmapheresis—Bloodletting Revived and Refined

During several centuries one of the chief therapeutical methods besides the administration of herbs was attempts to remove noxious substances from the body. This was performed either by purgation, often with drastic laxatives, or still more dramatic by bloodletting. It is said that several important persons, for instance the French king Louis XIII, were probably killed by such therapy. Fifty years ago we were still taught that bloodletting might be valuable in certain states of cardiac decompensation, but the advent of rapidly acting diuretics has made even this last remnant of acute phlebotomy obsolete. In recent years, however, removal of plasma by so-called plasmapheresis has become highly fashionable. The risks of an overzealous application are as great or even greater than they were regarding phlebotomy, but there is no question that selected patients may be much improved by such treatment. It may even be life saving.

Initially I should like to stress that the word plasmapheresis consists of two halves, plasma and apheresis, a Greek word that means removal. The etymological hyphenation should therefore be plasm-apheresis. The correct spelling is also leukapheresis, not leukophoresis, when white cells are removed and utilized.

As early as 1947 Lerner and Watson (3) described the occurrence of what they called cryoglobulin, i.e. globulin that precipitates on cooling. Such precipitation had been described before as stratification of serum or complete gelification (8). This author determined serum viscosity at different temperatures and found sera with very rapid increase at low temperatures but without the formation of precipitates. Together with Willert we tried plasmapheresis on a patient with macroglobulinemia in 1955 and were able to show that the macroglobulin content could be diminished, but our technique was not radical enough. John Fahey and his group in Bethesda performed very massive plasmapheresis on some patients with highly viscous serum containing large amounts of macroglobulins with excellent clinical results (7). At this time the technique with plastic bags was used and the separation of plasma from the red cells was a complicated and very time-consuming business.

The advent of the cell separator changed this completely and it became easy to withdraw large quantities of plasma separated from the cells. The indications for removal of plasma and the following substitution with normal plasma or human serum albumin have increased considerably during the last years. It has been found that the high viscosity may be detrimental in several ways. Strangely enough the high viscosity in itself that should cause mechanical hindrance of the circulation with an increased load upon the heart is rare, even if convincing results after plasmapheresis have been described. It seems to be a paradox that the blood is diluted in hyperviscous states, but this is a fact. Many of these patients suffer from considerable anemia and have even been treated with blood transfusions when the opposite method, removal of plasma, should have improved the so-called anemia. The volume of total erythrocytes may be practically normal whereas the plasma volume may be doubled. We have been able to observe this and have seen a cure of anemia after removal of 10 liters of plasma. The third and perhaps most important symptom in the hyperviscosity syndrome is the bleeding tendency. Already in the first publication on macroglobulinemia we described nosebleeds, oozing of blood from the gums, and intraocular bleedings. As a matter of fact this is one of the most important clinical symptoms. It occurs also in a few patients with a very high content of viscous IgG produced by myeloma cells. The picture in the eye grounds and the bleeding from the mucous membranes are therefore general signs of hyperviscosity, and it should be remembered that one of the most important diagnostic procedures is ophthalmoscopy. The recognitions of what I have called fundus viscoproteinemicus are of great practical value.

Regarding indications for removal of plasma it

may be said that this should only be used in severe conditions with marked hyperviscosity when rapid improvement is necessary The method is not a treatment of the underlying disease and it is clear that this should be attacked by cytostatic drugs and possibly also by glucocorticoids Before the advent of active plasmapheresis on a grand scale we have seen very marked reduction of a high plasma viscosity during treatment with chlorambucil or melphalan with lasting results regarding the viscosity syndrome even if it takes a long time to obtain such results

Another type of cryoglobulinemia has recently been the subject of intense study These patients have smaller amounts of cryoglobulin and this is formed by immune complexes These usually contain an active IgM that is regarded as an antibody against IgG In the classical case the IgM is monotypical and is probably produced by one clone of cells The condition is then an instance of macroglobulinemia with the formation of an immunologically active IgM This may well be compared to rheumatoid factor activity and as a matter of fact it is a characteristic of such sera that they have a high titer of so called rheumatoid factor The clinical picture in this syndrome is characterized by purpura arthralgia and often involvement of the kidneys Sometimes a picture of polyangeitis nodosa is also seen and the first authors to study the occurrence of cryoglobulins in different clinical conditions found some patients with this disease (4)

The story of these immune complexes has recently become still more complex when it was found that a large number of these patients had liver disease with evidence of infection with hepatitis B virus A recent study from Franklin s Laboratory at the NYU showed that 74% of the cryo precipitates contained either the antigen or its antibody Four precipitates were examined by electron microscopy and virus particles were found in all It is well known that there is a connexion between hepatitis B virus and polyangeitis nodosa but it is quite obscure why the immune response to the virus may result in IgM anti IgG giving characteristic cryoglobulins To my mind this is one of the most fascinating developments in recent studies of infectious diseases the damage may be caused not so much by the infectious agents as by the response of the body to the infection New such examples are being discovered every year (4)

It is clear that all immune complexes are not cold precipitable Some years ago we treated two patients who were sent to us because they had a severe hyperviscosity syndrome with anaemia spuria and a markedly increased plasma volume One of these patients was treated with plasmapheresis and was much improved The sera contained immune complexes of different sizes It is possible that these conditions are not readily recognized by the clinicians and we have only seen these two patients with the condition in amplissima forma Their histories have been published (6)

The most fascinating application of bloodletting with the new techniques regards another type of disease The number of patients who are suffering from deficiencies because of antibodies against metabolically important substances is ever increasing A special group is formed by patients who suffer from severe bleeding tendency because they have developed antibodies against some coagulation factor These conditions are extremely difficult to treat because the antibody neutralizes exogenous clotting factors administered intravenously Usually these antibodies arise spontaneously They are true autoantibodies but the facts regarding their possible monoclonality have not yet been settled The few instances where this has been definitely demonstrated would be compatible with the hypothesis that fortuitously a special clone of immunoglobulin producing cells proliferates They would thus belong to the so called monoclonal gammapathies In some other conditions the patients suffer from classical autoimmune disease such as SLE and then the immunoglobulin production is polyclonal

Sick receptors on cell surfaces is an interesting subject that has lately become very fashionable J Roth and Quatrecasas were the first authors who realized that marked refractoriness to insulin may be caused not only by circulating antibodies against the hormone Such antibodies can be detected in vitro by their activity in neutralizing the effects of insulin It has been demonstrated beyond doubt that there are also patients who are resistant against very large doses of insulin and still have no freely circulating antibodies against the hormone It seems pretty clear that antibodies may bind to the insulin receptors on the cells and thus cause a block I feel convinced that this concept of receptor blocking by specific antibodies will become one of the most fruitful fields for extended studies in the future

Another similar situation is probably related to the development of myasthenia gravis Many authors have maintained that this disease has an immunological background and it is well known that the thymus is in some cases implied in the pathogenesis Antibodies against the acetylcholine receptor on the neuromuscular junction are probably responsible for the disease in a majority of cases

The best proof that this theory is correct may of course be obtained if massive plasmapheresis would be successful A number of such patients have now been observed and as usually the enthusiasm was very great initially whereas the present opinion is more balanced (2) Even if the practical value of the method may be discussed there is no question about the fact that plasmapheresis strongly influences the severity of the disease and the next years will teach us the correct selection of cases and the best technique Theoretically attractive is the hypothesis that massive plasmapheresis should be followed by a course of cytostatics for instance azathioprine in order to damage the clone(s) that produces the antibody It may perhaps be specially vulnerable after decided lowering of its product i e the noxious IgG and cytostatic treatment should therefore be given directly after plasmapheresis Similar ideas may of course be applied to the rare cases with refractoriness against insulin when this is caused by an autoantibody against the receptor

The discussion about cytotoxic antibodies in autoimmune disease has been very lively during the last decades especially regarding SLE Attempts to influence the symptoms in this disease by plasmapheresis have been made but do not seem to have been successful There is however another condition where the effects from removal of an autoantibody seem to have been excellent

Goodpasture s syndrome is a rare condition with chronic purpura of the lungs (so-called hemosiderosis pulmonum) with repeated hemoptyses combined with a renal disease that is often fatal In some instances the pulmonary damage occurs alone and may be diagnosed clinically (9) It is also in itself a serious disease Immunological studies have detected the presence of an autoantibody against basement membrane both in kidney and lungs There is obviously a chemical similarity or identity between some constituents of this membrane in both organs Several reports seem to indicate that massive plasmaphereses really improve the situation Combined with cytostatics it may even cause remissions or possibly cures (5)

It is interesting to realize that complete Goodpasture s syndrome is not always present In 1944 the present author described the clinical diagnosis of a patient with the typical picture of hemosiderosis pulmonum who had been seen in Uppsala (8) In 1948 the literature on pulmonary hemosiderosis was collected and at that time nothing was known about the combination with renal disease Later I have seen in various countries examples of pure hemosiderosis pulmonum and it is quite evident that a number of patients who should be treated and possibly saved by plasmapheresis will occur in departments of medicine and pneumonology as obscure hemoptysis with widespread pulmonary infiltrates It will be interesting to see when the first patient with purely pulmonary symptoms will be treated successfully Also the pediatricians have published observations of this disease

Even if there can be no question about the fact that plasmapheresis as a new form of bloodletting has come to stay as an important therapeutic procedure we must remember that the indications should be very clear before we start The method is not without risks if complications are not observed and corrected at an early stage The method is extremely expensive both as regards plasma substitutes (fresh plasma serum albumin) and above all regarding man power The method should only be used on very strong indications It is not a cure of macroglobulinemia or myeloma but may have a place in alleviating severe symptoms in two stages of these diseases 1) The acute stage if severe hyperviscosity is present and needs quick relief until cytostatics have given results 2) The final stage when hyperviscosity recurs and the bone marrow has been so severely damaged either by the disease or by previous therapy that this can no longer be continued

Jan G Waldenstrom

REFERENCES

1 Behan P O et al Plasma-exchange combined with immunosuppressive therapy in myasthenia gravis Lancet 2 438–440 1979

2 Davis J N et al Long term effects of repeated plasma-exchange in myasthenia gravis Lancet 1 464–468 1979

3 Lerner A B & Watson C J Studies of cryoglobulins I Unusual purpura associated with the presence

of a high concentration of cryoglobulin (cold precipitable serum globulin) Am J Med Sci 214 410–415 1947
4 Levo Y Franklin E C et al Mixed cryoglobulinemia—an immune complex disease often associated with hepatitis B virus infection Trans Assoc Am Physicians 90 167–173 1977
5 Lockwood C M et al Reversal of impaired splenic function in patients with nephritis or vasculitis (or both) by plasma exchange N Engl J Med 300 524–530 1979
6 Nyman M & Hansson U B In Human and anti human gamma globulins (ed R Grubb) Pergamon Press Oxford 1971
7 Solomon A & Fahey J L Plasmapheresis therapy in macroglobulinemia Ann Intern Med 58 789–800 1963
8 Waldenstrom J G Incipient myelomatosis or "essential fibrinogenopenia—a new syndrome? Acta Med Scand 117 216–247 1944
9 — Pulmonary hemosiderosis In Modern trends in diagnostic radiology pp 86–93 Butterworth London 1948

BOOK REVIEW

Bradykinin Kallidin and Kallikrein Handbook of Experimental Pharmacology vol XXV Supplement Edited by E G Erdos 656 pages with indexes 817 Sw cr 1274 Springer Verlag Berlin Heidelberg and New York 1979

The same subject was covered in vol XXV in the Handbook of Experimental Pharmacology series published in 1970 During the last decade research within this field has been quite rapid and an updating edition is highly adequate The new volume is most impressive both from qualitative and quantitative point of view The book is organized in 17 chapters written by well known investigators in the respective fields They deal with various aspects from basic and clinical point of view

The first chapters are mainly concerned with the biochemistry of kininogenases i e the enzymes releasing kinins and their inhibitors and also discuss closely related systems These parts are of special value for investigators actively engaged in research but serve also as a basis for the physiological and clinical aspects presented in the following sections Of particular clinical interest and relevance are chapters dealing with plasma kallikreins kininases renal kallikreins and bradykinin–prostaglandin interactions

The interrelations between the plasma kallikrein kinin system blood clotting the complement system and the fibrinolytic system have to a great extent been clarified during the last few years This is of importance with respect for instance to isolation and purification of plasma components to be administered to patients with various deficiencies

Kinin degrading enzymes kininases attract considerable interest because of the recent finding that kininase II is identical with the angiotensin converting enzyme Inhibitors of kininase II decrease blood pressure in renovascular hypertension and also in many cases of essential hypertension particularly those with elevated plasma renin activity This has lead to a new intriguing approach in antihypertensive therapy

The renal kallikrein kinin system has been extensively studied during the last decade 50 years after the original description of the urinary kallikrein The role of this system in renal handling of electrolytes and water and in blood pressure regulation is thoroughly penetrated by Ward and Margolius and also by Mills

The finding by Vane in 1971 that aspirin like drugs inhibit prostaglandin synthesis has lead to intense research within this field and it has become clear that mai effects of bradykinin are mediated by prostaglandins T current knowledge in this area has been summarized I Terragno

In general the various chapters are well written ai clear both with respect to text tables and illustrations most instances the authors have included an impressi number of references Actually the author index contai more than 6 000 references altogether and the subject i dex covers 76 pages

In conclusion this volume is of major general intere and value as a handbook for investigators in the fiel However in view of the increasing importance bradykinin kallidin and kallikrein for the understanding various pathological states it can also be recommende for doctors working in various areas of clinical medicine

Lennart Hulthen and *Bernt Hokfelt* Malmo Sweden

On Acquired Hemophilia A

A Survey of 11 Cases

Inga Marie Nilsson and Stefan Lamme

From the Coagulation Laboratory Malmo General Hospital Malmo Sweden

ABSTRACT Acquired hemophilia A due to antibodies of factor VIII procoagulant activity is rare This paper reports 11 such patients followed up for long periods They exemplify various forms of associated disorders Four of them have died from hemorrhages 4 have had complete remission and 3 are still alive with persistent inhibitors The inhibitor activity was recovered in the immunoglobulin fraction in all the patients studied Various forms of treatment were tried but remission related to therapy was seen in only one woman affected post partum Spontaneous remissions are common and the aim of therapy must be to control acute severe hemorrhage

Key words acquired hemophilia factor VIII antibodies factor VIII IgG

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Acquired hemophilia A is a rare defect of blood coagulation due to the development of antibodies to factor VIII procoagulant activity (VIII C) These inhibitors have been referred to as spontaneous to distinguish them from the inhibitors of VIII C which may complicate hemophilia A and which are due to transfusion of blood or factor VIII concentrates

The first case was reported in 1940 by Lozner et al (14) In 1950 Deutsch (5) published a monograph on the disease and suggested the term Hemmkörper Hämophilie Margolius et al (15) gave a classical review of this subject in 1961 Today at least 100 cases are on record (28) Most of them have however been followed up for only a relatively short time

Patients with spontaneous inhibitors of VIII C have had co-existing established or assumed immunological disorders such as collagen diseases (e g lupus erythematosus) (15 27) drug reactions (e g penicillin) (1 8 12 15 24) certain neoplasms skin diseases (e g pemphigus and psoriasis) (4 9) But inhibitors may also develop in women post partum (15 16 20 32) and in otherwise healthy elderly persons (15 26)

In several respects the bleeding manifestations of acquired VIII C deficiency resemble those in severe hemophilia The hemorrhages are often life threatening and very difficult to treat since infused factor VIII is rapidly inactivated by the inhibitor Still a patient may have no significant symptom for weeks or even months despite the persistence of the anticoagulant

Various forms of treatment have been suggested but as some patients with factor VIII antibodies recover spontaneously it has been very difficult to assess the therapeutic effect of any form of treatment (30)

This paper reports 11 cases of acquired hemophilia seen at our laboratory and followed up for long periods They exemplify various forms of associated disorders The inhibitor activity was recovered in the immunoglobulin fraction in all the patients studied Various forms of therapy were tried but without any demonstrable effect on the inhibitor level

METHODS AND MATERIALS

Laboratory methods

The factor VIII coagulant activity (VIII C) of plasma and concentrates was assessed from its normalising effect on the recalcification time of platelet rich hemophilia A plasma possessing less than 1% of the normal amount of VIII C The factor VIII level found was expressed relative to that in a normal standard consisting of pooled plasma from 20 healthy persons (17)

Inhibiting effect of patient's plasma on the recalcification time of normal plasma (simple anticoagulant test)

Abbreviations VIII C = factor VIII procoagulant activity VIIIR Ag = factor VIII related antigen APT = activated partial thromboplastin time

Table I *Clinical data on the patients*

Cf=cyclophosphamide Az=azathioprine

Case no	Debut	Age at debut (y)	Sex	Associated illness	Therapy	Course
1	1950	42	♀	Dysproteinemia	Steroids no effect	Died after 4 years from bleeding
2	1968	81	♀	Temporal arteritis	None	Died after 2 months from bleeding
3	1956	30	♀	Post partum	Steroids ACTH	Recovery after 8 months in association with ACTH therapy Delivery after 8 years Healthy after 23 years
4	1965	45	♂	Drug reaction (cloxacillin)	Steroids no effect	Died from bleeding after 1 month
5	1975	71	♂	Cancer	F VIII + Cf no effect	Spontaneous remission after 12 months Healthy after 4 years
6	1968	59	♀	None	Az + steroids F VIII + Cf	Alive after 11 years Lasting inhibitor
7	1975	75	♂	None	Cf + Az + steroids transitory effect later no effect	Alive after 4 years Lasting inhibitor
8	1978	72	♂	None (psoriasis)	Cf + steroids	Alive after 1 year Lasting inhibitor
9	1975	61	♀	None (psoriasis)	F VIII + Cf no effect	Spontaneous remission after 3 months No relapse after 4 years
10	1978	80	♀	None (polycythemia)	Cf + steroids	Spontaneous remission during first month No relapse for 1 year
11	1964	79	♂	None	Steroids no effect	Died from bleeding after 1 year

Normal plasma in a volume of 0 2 ml and a similar volume of the plasma to be tested in various dilutions were incubated for 3 min at 37°C after which 0 2 ml 0 03 M $CaCl_2$ solution was added and the clotting time was determined The highest dilution of the patient s plasma that prolonged the recalcification time was taken as the anticoagulant titre

Quantitative determination of factor VIII inhibitor Various dilutions of the plasma to be tested (0 6 ml) were incubated with 0 2 ml of a factor VIII concentrate (3 units of VIII C/ml) at 37°C for 2 hours As a blank 0 6 ml hemophilia A plasma (less than 1% VIII C and no anticoagulant) was incubated in the same dilutions as the plasma to be tested with 0 2 ml of the factor VIII concen

Table II *Results of the coagulation analyses*

Case no	Platelets (10^9/l)	Bleeding time (min) Duke	Ivy	Coagulation time (min)	APT time (sec)	VIII C (%)	VIIIR Ag (%)	P&P (%)	Fibrinogen (g/l)	F V (%)
1	165	4		120				80	3 7	
2	186	2	16	130		0		100	3 9	95
3	318	4		178		0		118	4 3	100
4	246	5		105		0		72	6 2	84
5	400	2		30	83	<0 5	196	42	3 6	95
6	206	4		>60	90	<0 5	280	118	4 6	98
7	238				122	<2 5	>400	124	4 3	190
8	200		5	>720	100	<2 5	204	116	3 2	123
9	266		11	125	82	<2 5	210	136	4 8	100
10	800	2	6	40	60	<2 5	280	95	5 2	104
11	338	*2*		86		0		*100*	*Normal*	*89*
Normal values	125–340	1–5	6–12	6–14	<45	60–160	60–175	80–120	2 0–4 0	80-

trate Following incubation the blank and the mixtures of plasma and factor VIII were assayed for residual VIII C in the way described above The inhibitor activity of the plasma was expressed as the number of units of VIII C (1 unit of VIII C is defined as the amount of VIII C present in 1 ml normal plasma) inactivated by 1 ml of the plasma

Factor VIII related antigen (VIIIR Ag) was determined immunologically in the way described by Holmberg and Nilsson (10) The platelet count bleeding time (Duke and Ivy) coagulation time activated partial thromboplastin time (APT time) factor XI factor IX P&P (prothrombin factors VII and X) factor V and fibrinogen were determined as described elsewhere (17)

Factor VIII concentrates 1) Human fraction I–O prepared by Kabi (AHF Kabi) according to the glycine method of Blomback and Blomback (3) One bottle (100 ml) contains approximately 300 units of VIII C 2) Hemate (Hyland method 4) One ampoule (30 ml) contains about 1 000 units of VIII C

Protein A Sepharose CL-4B gel was purchased from Pharmacia AB Uppsala Sweden Protein A is a cell wall constituent of certain strains of Staphylococcus aureus It selectively binds the Fc fragment of all IgG subclasses except IgG 3 (7 13)

Purification of IgG containing inhibitor of VIII C on protein A A column (10×150 mm) containing approximately 5 ml of packed protein A gel was used To avoid overloading we used 1 ml of the patient s plasma for every ml of the packed gel After elution of the first peak with 0.5 M NaCl the bound protein was eluted and appeared as a second peak with 0 1 M glycine HCl buffer at pH 2 4

CASE REPORTS

Clinical data on the patients and results of the coagulation analyses are given in Tables I and II

Case 1 has been described earlier (21) This was the first case seen in Malmo and was detected as early as 1950 At 9 years of age the patient a girl was found to have rheumatic fever Since the age of 29 she had had a collagen disease with hyperglobulinemia continuous fatigue bilateral pleurisy on several occasions and recurrent transient swellings of the joints but never with permanent deformities ESR about 100 mm/1 h

For several years she had bruised easily Bleeding after trauma had always been heavy but menstruation had been normal Later subcutaneous hematomas developed spontaneously The coagulation time had not been measured until 1950 when it proved to be prolonged—25 min (normal range 8–14 min) This prolongation was shown to be caused by a circulating anticoagulant of antihemophilic factor and was present in a titer of 1/10 On paper electrophoresis this anticoagulant was eluted from the gamma globulin fraction

Despite heavy steroid therapy the coagulation time gradually increased to 120 min The patient died in 1954 after bleeding from an ovarian cyst with rupture into peritoneal cavity resulting in peritonitis

Case 2 an 81 year-old woman with a history of pernicious anemia for 8 years and histologically verified temporal arteritis for 4 years who still required steroids because of the arteritis Three months before admission spontaneous hematomas and attacks of mucosal bleeding began to occur Laboratory studies revealed an inhibitor of VIII C in a titer of 1/10 Other coagulation studies electrophoresis and serological tests revealed nothing remarkable No therapy was given except steroids in the same dose as she had been receiving when the coagulation defect was detected The inhibitor remained unchanged Two months later she died of generalised bleedings

Case 3 a 32 year-old woman has been described earlier (20) Three months after delivery of her first born she had noticed subcutaneous bleedings on her right lower leg without known previous trauma During the next 5 months painful ecchymotic areas appeared on various parts of the limbs On admission she was found to have an anticoagulant of VIII C in a titer 1/100 Preparative electrophoresis demonstrated the inhibitor in the gamma globulin fraction

She received steroids for one month with no demonstrable effect but a few days after institution of ACTH in a dose of 40 U a day the coagulation time became shorter and the anticoagulant decreased After one month 8 months after onset of the subcutaneous bleedings VIII C was normal

Eight years later she gave birth to her second child without any complications She has not had any relapse for over 23 years

Case 4 was a 45 year-old man with tuberculosis for which he had undergone an operation with segmental resection of the left lung Postoperative wound infection was treated with chloramphenicol and cloxacillin An antibiotic reaction with fever toxicodermia and joint symptoms developed Five weeks later he had severe bleeding symptoms The coagulation time was more than 150 min and an anticoagulant of VIII C in a titer of 1/5 was demonstrated After another month during which he was given large doses of steroids he died from abdominal hemorrhagia with 7 liters of blood in the peritoneal cavity

Case 5 was a 71 year-old man who had been operated on for cancer of the large bowel 6 months before admission He was admitted to hospital with a huge sublingual

ıhibitor ıter U/ml)	Plasma proteins	Serology
10	Hypergamma	AST pos
10	Gamma at lower limit	Normal
100	Normal	Normal
5	Low albumin	AST ASTA pos
I	Infl reaction IgG 26 g/l	Normal
)0	Normal	Normal
3	Low haptoglobin	Normal
)0	2 small cathodal bands	Normal
5	Normal	ANF pos (1/32)
5	Low haptoglobin	Normal
10	Normal	Normal

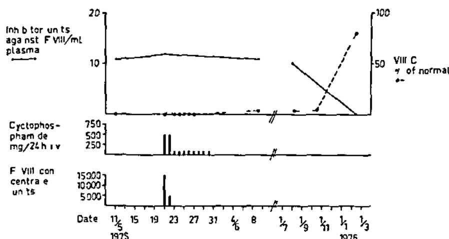


Fig 1 The course in case 5

hematoma and coagulation studies revealed an inhibitor of VIII C in a concentration of 11 U/ml The inhibitor could be neutralised by anti IgG serum but not by serum against IgM or IgA

He was treated according to Green (9) with factor VIII (Hematrate) in a dose of 15 300 U and cyclophosphamide 500 mg i v on the first day and 5 000 U of factor VIII and 500 mg cyclophosphamide on the second followed by cyclophosphamide 100 mg/day for the next 8 days However this treatment failed to neutralise the inhibitor or to raise the VIII C level (Fig 1) The inhibitor was not affected by this treatment

Nine months later the inhibitor disappeared spontaneously (Fig 1) and has not re appeared during the last 4 years

Case 6 a previously healthy 59 year old woman has been described earlier (19) In Jan 1968 she had a depression and was given amitriptyline In July 1968 subcutaneous bleedings and muscle hematomas appeared without any known previous trauma Her coagulation time was prolonged and an inhibitor of VIII C was observed in a titer of 1/10 Serological tests as well as electrophoresis revealed nothing remarkable Large doses of steroids for 12 weeks combined with azathioprine during the last 3 weeks did not result in any improvement

In 1971 the titer of the inhibitor had risen to 1/20 which corresponded to 162 U/ml Though inhibitor in suc a high concentration cannot be neutralised by factor VII treatment with cyclophosphamide combined with fact VIII was tried But her inhibitor concentration remaine very high—80 U/ml

Since 1971 she has not received any therapy Thoug she does her utmost to avoid even the slightest traum she still has repeated hemorrhages into muscles and joint When last measured at the end of 1979 the inhibitor wa still 150 U/ml

Case 7 a 75 year old man who had always felt well I Jan 1975 he noticed that he began to bruise readily an had muscle hematomas in his left arm and leg On admi sion to his local hospital he was in a very poor conditior His coagulation time was prolonged and he had a circula ing anticoagulant On two occasions he was treated wit 500 mg cyclophosphamide i v but was not given an factor VIII concentrate His coagulation time becam normal within 14 days

In Aug 1976 hemorrhages recurred but this time the were refractory to cyclophosphamide steroids an azathioprine He had an inhibitor of VIII C in a concentra tion of 18 U/ml

The patient has not had any noteworthy hemorrhage

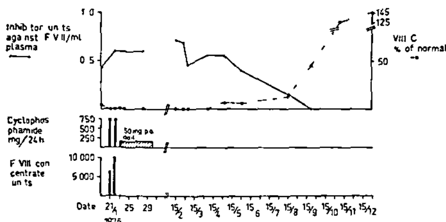


Fig 2 The course in case 9

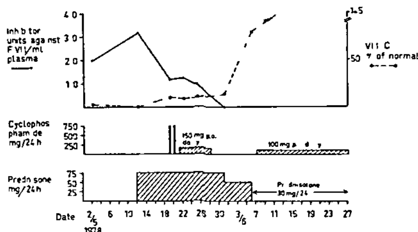


Fig 3 The course in case 10

since then but he still has his coagulation defect He had no associated illness or drug reaction and electrophoresis has not shown anything remarkable

Case 8 a 72 year-old man with mild psoriasis and 2–3 years history of mild arthritis which was thought to be psoriasis arthropathia In Jan 1978 he noticed that he bruised readily and increased fibrinolysis was suspected at his local hospital Treatment with Cyclokapron® resulted in a very slow decrease in his bleeding tendency

Seven months later he developed huge hard hematomas in the right arm back and legs Coagulation studies showed an excessively high activity of an inhibitor of VIII C—300 U/ml

He was treated with cyclophosphamide for 4 months without any demonstrable effect He has not had any severe bleeding in the last 12 months

Case 9 a 61 year-old woman who had psoriasis but had always felt well She complained of pain in her right lower leg and her general practitioner had prescribed oral indomethacin and bandaged her leg Later removal of the bandage revealed a large hematoma A few days later she developed hematuria and was admitted to hospital She proved to have an inhibitor of VIII C—0 5 U/ml

She was treated with a total dose of 16 300 U of factor VIII and 1 500 mg cyclophosphamide divided between 2 days followed by cyclophosphamide 150 mg a day (Fig 2) In spite of the large factor VIII dose VIII C reached only 7 5% immediately after the infusion on day 2 but after 24 hours it was still as high as 3% indicating that the inhibitor was temporarily neutralised However after one week the inhibitor was as high as before treatment Four months later the inhibitor began to decrease and after another 4 months it was no longer demonstrable (Fig 2) She has not had any relapse for over 2 years Electrophoresis had revealed nothing remarkable She had a low antinuclear antibody titer viz 1/32

Case 10 an 80-year-old woman who had passed blood stained stools for two periods in the last year Roentgenograms of the stomach and intestines were normal Admitted to hospital with a huge hematoma on her right arm Coagulation tests showed a low factor VIII—less than 2 5% and an inhibitor of VIII C

The bleeding continued and she was given 8 U blood and steroids After 2½ weeks treatment with cyclophosphamide combined with steroids was instituted During the last week before the institution of cyclophosphamide the inhibitor had already fallen from 3 5 to 1 U/ml indicating that cyclophosphamide could hardly have affected the course The inhibitor disappeared within 3 weeks (Fig 3) She has had no recurrence during follow up (18 months) but polycythemia vera has since been diagnosed

Case 11 was a 79 year-old man who had had a myocardial infarction 12 years earlier Admitted to hospital with a hematoma in his right arm Examination at his local hospital revealed prolonged coagulation time Three weeks later he had several hematomas on the chest and legs and he was given 2 U blood After transfer to our hospital he was shown to have an inhibitor of VIII C in a titer of 1/10 He was treated with steroids without any demonstrable effect He died from a bleeding complication one year after the onset of the first symptoms

RESULTS OF IgG STUDIES IN CASES 6 AND 8

Protein A Sepharose was used in cases 6 and 8 for purification of IgG In both cases practically all inhibitor activity from the applied plasma was recovered in the eluted IgG fraction

In case 8 electrophoresis showed 2 very small cathodal bands IgG in 0 0175 M phosphate buffer pH 6 5 was chromatographed on a DEAE Sephadex A 50 column equilibrated and eluted with the same buffer On agarose electrophoresis the first portion of the eluate (fractions 15–36) contained the cathodal bands but later fractions eluted with 0 5 M NaCl did not contain these bands The inhibitor activity of fractions 15–36 was 9 U/mg protein and in

the later fractions eluted with 0 5 M NaCl 15 U/mg protein This proved that the inhibitor activity was not confined to the cathodal bands

DISCUSSION

Inhibitors to VIII C have practically always been gammaglobulin immunoglobulins which are not monoclonal The only known exceptions are one IgA myeloma case and two IgM cases (28)

In cases 1 and 3 of this study preparative electrophoresis showed that the inhibitor could be eluted from the gammaglobulin fraction In case 5 it was possible to neutralise the inhibitor by an anti IgG serum In cases 6 and 8 IgG was purified from plasma and contained all the inhibitor activity No monoclonal distribution of the inhibitor was found in case 8 in spite of the fact that electrophoresis had shown 2 small M components

Most spontaneous inhibitors have both κ and λ light chains while inhibitors in hemophiliacs are usually of one light chain type usually κ (28)

Patients with inhibitors of factor VIII procoagulant activity have a severe and often fatal bleeding disorder In most published cases the course of the disease was not followed up very long Of our 11 patients 4 died from hemorrhages 4 had complete remissions and 3 are still alive with persistent inhibitors

All the patients who died had relatively low inhibitor titers Two of them died already within the first two months of the onset of their disorder Steroid therapy had no effect and one of the patients was already receiving steroids when the bleeding disorder started Two of them had collagen diseases one had a severe drug reaction and one was an elderly previously healthy man

Also 3 of 4 patients who had a remission had low inhibitor titers ($\leq$1/10) Two of these patients had no associated disorder and the third had been operated on for cancer 6 months earlier In one case the inhibitor had begun to decrease before treatment with cyclophosphamide was started (Fig 3) In two cases treated according to Green (see below) the inhibitor was not affected Four and 9 months later respectively the inhibitor disappeared spontaneously (Figs 1 and 2) In the fourth case the inhibitor appeared post partum The patient had a titer of 1/100 and the inhibitor disappeared promptly in association with ACTH therapy In this case we cannot exclude the possibility of a spontaneous remission because the prognosis is relatively favou ble and the inhibitor often disappears spontaneou ly in cases appearing post partum (16 32) T patients with persistent inhibitors are alive 1 4 a 11 years after onset of the condition They have h the highest inhibitor concentrations and two them have now inhibitor in an extremely high co centration None of them have had any associat disorder

Judging from our material patients with a lo inhibitor level have a better chance of having remission than those with a high level but the ea mortality is not lower In fact 6 of 7 patients w low inhibitor levels were either in remission or de one year after the first onset of the symptoms

Several drugs and treatment regimens have be tried but owing to a variety of associated disorde and the variable course of the inhibitor cauti must be exercised when making any conclusions seems important to control an associated disord (6) and in patients with underlying collagen diso ders the inhibitors may disappear on treatment wi steroids or other immunosuppressive drugs (27 3 33)

In patients without underlying diseases trea ment with steroids will usually not affect the i hibitor concentration (11 15 34) Treatment wi chemotherapeutics alone or combined with stero has occasionally resulted in complete disappea ance of factor VIII antibodies (29 34) but su therapy is usually of little or no value (9)

Green (9) reported in 1971 a 54 year old wom with inhibitor of factor VIII She was initial treated with a combination of methotrexat azathioprine and cyclophosphamide but witho improvement Rapid administration of 10 000 U factor VIII in combination with a large dose of i cyclophosphamide resulted *later in a prompt de*crease and disappearance of the inhibitor

We have not seen any beneficial effect of th different types of therapy except for one woma affected post partum Our negative results of trea ment according to Green might be explained by th fact that in at least two cases we could not infus sufficient factor VIII to neutralise the inhibitor

Since one cannot affect the inhibitor level by th different forms of treatment which we have tried one must anyhow try to achieve hemostasis when patient has a severe hemorrhage We are inclined t treat patients with low inhibitor levels in an acut bleeding according to Green with large doses o

factor VIII combined with cyclophosphamide (9) Patients with high levels of inhibitors are almost impossible to treat However plasmapheresis can lower the inhibitor titer sufficiently to make re placement therapy possible Such a case has been described by Pintado et al (23) An interesting method is to use for example Aminco plasma pheresis apparatus in combination with large Protein A Sepharose columns Using this method only the IgG is absorbed and the plasma can be returned to the patient

Another possibility might be treatment with activated factor IX Various factor IX preparations can reportedly secure hemostasis in hemophilic patients with inhibitors of factor VIII (2 25) Nevertheless Parry and Bloom (22) did not find recently any therapeutic effect of FEIBA (Immuno Austria) on 14 separate bleeding episodes

ACKNOWLEDGEMENT

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REFERENCES

1 Andersen B R & Troup S B IgG antibody to human antihemophilic globulin (factor VIII) J Immunol 100 175 1968
2 Blatt P M White G C McMillan C W & Roberts H R Treatment of anti factor VIII antibodies Thrombos Haemostas 38 514 1977
3 Blomback B & Blomback M Purification of human and bovine fibrinogen Arkiv Kemi 10 415 1956
4 Cooke J V Anderson J B & Gamble W S Circulating factor VIII anti-coagulant in bullous dermatitis Arch Intern Med 110 511 1962
5 Deutsch E Die Hemmkörper Hamophilie Springer Verlag Wien 1950
6 Ellis H Handley D A & Taylor K B Surgery in a patient with an acquired anticoagulant Lancet 1 1167 1959
7 Forsgren A & Sjoquist J Protein A from Staphylococcus aureus I Pseudoimmune reaction with human globulin J Immunol 97 822 1966
8 Green D Spontaneous inhibitors of factor VIII Br J Haematol 15 57 1968
9 — Suppression of an antibody to factor VIII by a combination of factor VIII and cyclophosphamide Blood 37 381 1971
10 Holmberg L & Nilsson I M Genetic variants of von Willebrand s disease Br Med J 3 317 1972
11 Horowitz H I & Fujimoto M M Acquired hemophilia due to a circulating anticoagulant Am J Med 33 501 1962
12 Klein K G Parkin J D & Madaras F Studies on an acquired inhibition of factor VIII induced by penicillin allergy Clin Exp Immunol 26 155 1976
13 Kronwall G & Williams R C Differences in anti protein A among IgG subgroups J Immunol 103 828 1969
14 Lozner E J Joliffe L S & Taylor F H L Hemorrhagic diathesis with prolonged coagulation time associated with a circulating anticoagulant Am J Med Sci 199 318 1940
15 Margolius A Jackson D P & Ratnoff O D Circulating anticoagulatns a study of 40 cases and a review of the literature Medicine 40 145 1961
16 Michiels J J Bosch L J van der Plas P M & Abels J Factor VIII inhibitor postpartum Scand J Haematol 20 97 1978
17 Nilsson I M Haemorrhagic and thrombotic diseases Wiley London 1974
18 Nilsson I M Blomback M & Ahlberg Å Our experience in Sweden with prophylaxis on hemophilia Bibl Haematol 34 111 1970
19 Nilsson I M Hedner U & Holmberg L Suppression of factor VIII antibody by combined factor VIII and cyclophosphamide Acta Med Scand 195 65 1974
20 Nilsson I M Skanse B & Gydell K Circulating *anticoagulant after pregnancy and its response to* ACTH Acta Haematol 19 40 1958
21 Nilsson I M & Wenckert A Hyperglobulinemia as the cause of hemophilia like disease Blood 8 1067 1953
22 Parry D H & Bloom A L Failure of factor VIII inhibitor bypassing activity (FEIBA) to secure haemostasis in haemophilic patients with antibodies J Clin Pathol 31 1102 1978
23 Pintado T Taswell H F & Bowie E J W Treatment of life threatening hemorrhage due to acquired factor VIII inhibitor Blood 46 535 1975
24 Poon M-C Saito H Ratnoff O D Forman W B & Wisnieski J Techniques for demonstration of the specificity of circulating anticoagulant against antihemophilic factor (factor VIII) with studies of two cases possibly related to diphenylhydantoin therapy Blood 49 477 1977
25 Preston F E Dinsdale R C W Sutcliffe D J Bardhan G Wyld P J & Hamlyn J F Factor VIII inhibitor bypassing activity (FEIBA) in the management of patients with factor VIII inhibitors Thromb Res 11 643 1977
26 Rizza C R Edgcumbe J O P Pitney W R & Child J A The treatment of patients having spontaneously occurring antibodies to anti hemophilic factor (factor VIII) Thromb Diath Haemorrh 28 120 1972
27 Robboy S J Lewis E J Schur P H & Colman R W Circulating anticoagulant to factor VIII Am J Med 49 742 1970
28 Shapiro S S & Hultin M Acquired inhibitors to blood coagulation factors Sem Thrombos Haemostas 1 336 1975
29 Sherman L A Goldstein M A & Sise H S Circulating anticoagulant (antifactor VIII) treated with immunosuppressive drugs Thromb Diath Haemorrh 21 249 1969
30 Shulman N R & Hirschman R J Factor VIII

inhibitors in non hemophilics In Hemophilia and new hemorrhagic states (ed K N Brinkhous) p 169 University of North Carolina Press Chapel Hill 1970
31 Sise H S Gauthier J Desforges J & Becker R *Spontaneous circulating anticoagulant (antifactor* VIII) case report and review of the literature Am J Med 32 964 1962
32 Voke J & Letsky E Pregnancy and antibody to factor VIII J Clin Pathol 30 928 1977
33 Whitfield A G W Meynell M J Fessey B M & Hudson W A A circulating anticoagulant occurring after temporal arteritis and controlled by corticosteroid therapy J Clin Pathol 15 357 1962
34 *Winkelman G Bottcher D & Groh R* A circulating anticoagulant directed against anti hemophilic globulin (factor VIII) combined with thrombocytopenia Thromb Diath Haemorrh 20 144 1968

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Lymphocytopenia Preceding Chronic Lymphocytic Leukemia

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ABSTRACT In 11 patients with an average peripheral blood lymphocyte count of $21.1\times10^9/l$ at the time of diagnosis of chronic lymphocytic leukemia (CLL) WBC and differential counts had been recorded on 1–26 occasions more than 5 years before the diagnosis The median lymphocyte count in the preleukemic period was $1.3\times10^9/l$, which is significantly lower than $2.4\times10^9/l$ found in a sex and age-matched control series In 3 patients lymphocytopenia coexisted with normal levels of serum immunoglobulins in the preleukemic period It is suggested that the preleukemic lymphocytopenia was mainly due to low numbers of T cells and that a deficiency in T lymphocytes may favour the development of the malignant, monoclonal B-cell proliferation characteristic of CLL

Key words chronic lymphocytic leukemia preleukemia lymphocytopenia

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The mechanisms behind the development of chronic lymphocytic leukemia (CLL) remain unclear (9) Attempts to analyse the preleukemic period might help to elucidate the pathogenesis of the disease

Recently we made a diagnosis of CLL in an elderly woman who had been hospitalized several times during the last 44 years because of diabetes mellitus According to her case records strikingly low lymphocyte count had been recorded repeatedly before the diagnosis of CLL We therefore decided to investigate whether lymphocytopenia may be a common phenomenon preceding the lymphocytosis characteristic of CLL

PATIENTS AND METHODS

Patients under observation or treatment for CLL at our departments were interviewed about previous medical examinations and efforts were made to obtain the relevant case records In 11 patients 4 female and 7 male aged 38–88 years and with lymphocyte counts of 10.6–$31.3\times10^9/l$ (median 21.1) at the time of diagnosis information was obtained on WBC and differential counts 5–44 years before the diagnosis of CLL The disorders requiring medical attendance in the preleukemic period are given in Table I The lymphocyte counts were calculated from the WBC and differential counts Lymphocyte counts recorded during treatment with corticosteroids were omitted In 3 patients the serum gammaglobulin concentration had been determined together with WBC and differential counts 6 10 and 12 years before the diagnosis of CLL

A control group was obtained through assessment of the lymphocyte counts in a series of consecutive patients investigated for mainly cardiac complaints in whom acute myocardial injury or other serious diseases could be excluded with reasonable certainty Two controls matched for sex and age were selected for each CLL patient studied in the preleukemic phase

RESULTS

WBC and differential counts had been recorded more than 5 years before the diagnosis of CLL in 11 patients Two or more observations were available in 6 patients (nos 1–6) in 5 (nos 7–11) the analysis had been performed only once (Figs 1 and 2) Lymphocyte counts below $1.5\times10^9/l$ had been recorded in the preleukemic period in 7 (64%) of the 11 patients Only 3 (14%) of the 22 controls had counts below this level

In Fig 3 the preleukemic lymphocyte counts are compared with the counts in the controls In this comparison the median value of the lymphocyte counts in each of the patients examined more than once was considered to represent the number of lymphocytes in the preleukemic period The median preleukemic lymphocyte count was 1.3×10^9 which is significantly lower than the median value of $2.4\times10^9/l$ found in the control group ($p<0.002$ Wilcoxon test)

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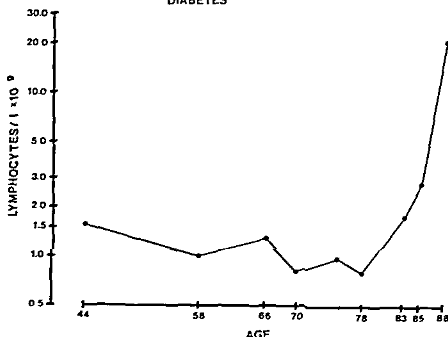


Fig 1 Lymphocyte counts before and at the time of diagnosis of CLL in a woman with diabetes followed for 44 years

In 3 patients gammaglobulin concentrations were assessed in the preleukemic period All had normal levels coexistent with lymphocytopenia (Table II)

DISCUSSION

The decreasing lymphocyte counts in case 1 (Fig 1) observed during a period of more than 30 years suggest that a reduction of the peripheral blood lymphocytes may precede the development of CLL The findings in the total series more than 5 years before the diagnosis of CLL indicate that lymphocytopenia may be common in the pre leukemic phase of CLL

The present retrospective study cannot show whether the low lymphocyte counts were due to a deficiency in any special subpopulation of lymphocytes In the controls the average lymphocyte count was 2.4×10^9/l In the peripheral blood of healthy subjects the number of immunoglobulin bearing lymphocytes i e B lymphocytes is about 0 2-0 7×10^9/l (6) The average preleukemic lymphocyte count of 1.3×10^9/l found in our patients is therefore hardly compatible with a selective deficiency in B-cells Moreover the findings of normal levels of

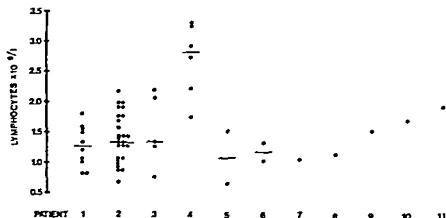


Fig 2 Preleukemic lymphocyte counts in patients 1–11 The median is indicated for patients with two or more assays

Table I *Clinical data on 11 patients examined more than 5 years before the diagnosis of CLL*

Pat no	Sex	Disease in pre leukemic period	Period studied before diagnosis of CLL (y)	Age at diagnosis of CLL (y)	Lymphocytes at diagnosis of CLL (×10⁹/l)
1	♀	Diabetes	5–44	88	21 5
2	♀	Discoid lupus	8–22	83	31 3
3	♂	Diabetes	12–14	70	13 4
4	♂	Diarrhoea cause unknown	7–24	56	25 5
5	♂	Pneumonia	6	57	21 7
6	♂	Temporal arteritis	10	72	18 4
7	♂	Bronchial asthma	7	62	10 7
8	♂	Duodenal ulcer	5	57	20 1
9	♂	Multiple sclerosis	7	38	20 2
10	♀	Diabetes	10	77	21 6
11	♀	Suspected but not verified pericardial cyst	11	76	21 1

serum immunoglobulins associated with lymphocytopenia suggest that the B lymphocyte functions were intact in the preleukemic lymphocytopenic phase It is therefore probable that the low lymphocyte counts were mainly due to a deficiency in T-cells

Although CLL is usually a B cell disorder of monoclonal origin (2 4) increased numbers of T lymphocytes have been demonstrated Catovsky et al (3) found that in a group of untreated stable CLL patients the number of T lymphocytes in peripheral blood was on an average 3 6×10⁹/l i e considerably higher than the lymphocyte counts recorded in the preleukemic phase of the present patients A minute T cell population in the preleukemic phase of CLL may therefore be considerably increased possibly as a reaction to the establishment of a malignant clone of B lymphocytes

There is experimental evidence that thymus-derived suppressor cells can restrict the proliferation of B lymphocytes and that an impaired T cell regulation of B cell proliferation may favour the development of autoimmunity and lymphoproliferative disorders (5) It has been suggested that in humans a defective T cell activity may be associated with the development of B cell neoplasms in patients infected with EB virus (8) Pronounced antigenic stimulation of B lymphocytes in patients with an impaired suppressor cell function may likewise promote the development of a lymphoproliferative disorder (7) It is therefore possible that viral or other stimuli causing an increased proliferation of B lymphocytes in a situation with coexisting deficiency in T-cells may increase the risk of development of a malignant clone of B-cells

Table II *Immunoglobulin concentrations and lymphocyte counts in 3 patients 6–12 years before diagnosis of CLL*

	Immunoglobulin concentrations	Normal values	Lymphocyte count (×10⁹/l)
Case 1	γ globulin 11 2 g/l	6 1–11 7	1 0
Case 6	γ globulin 12 3 g/l	6 1–11 7	1 0
Case 7	IgG 70 %	65–160	1 1
	IgA 115 %	50–160	
	IgM 155 %	30–200	
	(% of normal serum pool)		

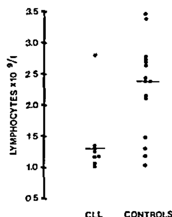


Fig 3 Lymphocyte counts in the controls and in the preleukemic period of 11 CLL patients The median is indicated for patients with two or more preleukemic counts

Lymphocytopenia i e *lymphocyte counts lower* than 1 5×10⁹/l (10) was found in 14% of the controls indicating that lymphocytopenia is not un*common in the general population CLL is a rela*tively rare disease and factors in addition to lymphocytopenia are therefore obviously necessary to bring about the malignant proliferation It may be that a deficiency in T-cells constitutes a risk factor for CLL Such a concept is supported by the facts that ageing is characteristically associated with a decrease in T lymphocytes (1) and that CLL patients are often old

REFERENCES

1 *Augener W Cohnen G Reuter A & Brittinger* G Decrease of T lymphocytes during ageing Lancet 1 1164 1974
2 Brouet J C & Seligmann M Chronic lymphocytic leukaemia as an immunoproliferative disorder Clin Haematol 6 1 169 1977
3 Catovsky D Miliani E Okos A & Galton D A G *Clinical significance of T-cells in chronic l*phocytic leukaemia Lancet 2 751 1974
4 Fialkow P J Najfeld V Lakshma Reddy Singer J & Steinmann L Chronic lymphoc leukaemia. Clonal origin in a committed B-lym cyte progenitor Lancet 2 444 1978
5 Gershwin M E & Steinberg A D Loss of pressor function as a cause of lymphoid maligna Lancet 2 1174 1973
6 Holm G Pettersson D Mellstedt H Hedfors & Bloth B Lymphocyte subpopulations in per eral blood of healthy persons Clin Exp Imm 20 443 1975
7 Louie S & Schwartz, R S Immunodeficiency the pathogenesis of lymphoma and leukemia Se *Hematol 15 117 1978*
8 Purtilo D T Szymanski I Bhawan J Yang S Hutt L M Boto W DeNicola L Maier Thorley Lawson D Fowler D & Troia, P *stein-Barr virusinfektions in the X-linked rece* lymphoproliferative syndrome Lancet 1 798 197
9 Sweet D L Golomb H M & Ultmann J E clinical features of chronic lymphocytic leukae *Clin Haematol 6 1 185 1977*
10 Wintrobe M M Clinical hematology 7th ed 1288 Lea & Febiger Philadelphia 1974

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Blood Pressure and Renal Function

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ABSTRACT The relationship between blood pressure (BP) and renal function was studied in samples of 49 year old men Of 3205 49 year old men, 2376 (74%) took part in a BP screening By systematic sampling, based on diastolic BP levels varying from very low to very high, 120 subjects were selected for this study Only subjects who were not on antihypertensive treatment were included Renal blood flow (RBF), renovascular resistance (RVR), glomerular filtration rate (GFR), filtration fraction (FF) and renal concentrating capacity were studied in 111 subjects none of whom had advanced hypertension With increasing BP there was a decrease in RBF ($r=-0\ 34$) and an increase in RVR ($r=0\ 81$) and FF ($r=0\ 35$) The changes in renal haemodynamics occurred gradually from low to high BP, and did not start at any particular BP level With increasing BP, GFR was unchanged An "autoregulation of GFR was thus found at all BP levels studied Renal concentrating capacity was unchanged These findings indicate that renal haemodynamics in essential hypertension are adjusted mainly to ensure a constant GFR

Key words essential hypertension glomerular filtration rate renal blood flow renal vascular resistance kidney concentrating ability epidemiology
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In 1938 Smith et al (39) presented the first study on renal function in essential hypertension in man using the clearance technique They found that renal blood flow (RBF) was less and the filtration fraction (FF) greater in hypertensive than in normal subjects Most of the hypertensive subjects had a normal glomerular filtration rate (GFR) In later studies varying findings have been obtained concerning RBF GFR and FF in essential hypertension Most studies have shown a decrease in RBF in all stages of the hypertensive disease (6 11 23) but in some studies RBF has been unchanged in early hypertension (16 24) In some studies GFR has been within the normal ranges (7 11 16) but a significant decrease also in GFR has been found in others However GFR has been less reduced than RBF leading to an increased FF

Maximal renal concentrating capacity in essential hypertension has been studied less Some investigators have found a marked decrease in concentrating capacity early in the hypertensive disease (15 30) whereas others (20) have found it normal until late in the disease

Thus the results regarding renal function in essential hypertension have been conflicting especially concerning the early stage of the disease The discrepancy in results has in many instances been due to differences in selection of patients especially with regard to duration and severity of the hypertension We have studied the renal function in an age homogeneous group of subjects in an attempt to define the functional changes in the earliest stages of the hypertensive disease

STUDY POPULATION

In order to find 120 subjects of the same age representing the entire range of blood pressure (BP) levels in the population every second 49 year old male resident in Göteborg (i e born 1926–27) was invited to participate in a screening examination of BP

The expected number of individuals in various diastolic BP (DBP) groups was calculated from the BP distributions

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Abbreviations RBF = renal blood flow FF = filtration fraction GFR = glomerular filtration rate BP = blood pressure DBP = diastolic BP SBP = systolic BP MAP = mean arterial pressure BSA = body surface area PAH = p-aminohippurate Cl_{PAH} = PAH clearance Cl_{in} = inulin clearance Cl_{cr} = creatinine clearance Hct = haematocrit RVR = renovascular resistance

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Table I *Plan for selection of subsamples from the 49 year old male population with regard to DBP and date of birth*

DBP at screening (mmHg)	Date of birth	Proportion of the population	Expected no of untreated subjects
<95	18	1/30	25
95–104	8 18	1/15	15
105–114	8 12 18 26 30	1/6	15
≥115	1–31	1/1	65

of earlier screening examinations of middle aged men in Goteborg (9) The selection plan included 1/30 of the subjects with a DBP at screening ≤95 mmHg 1/15 of those with DBP 95–104 mmHg 1/6 of those with DBP 105–114 mmHg and all subjects with DBP ≥115 mmHg This was achieved by systematic sampling based on the subjects date of birth (Table I) The days 8 12 18 26 and 30 were taken from a table of random numbers Subjects who met the criteria and were not on antihypertensive treatment were asked to participate in the investigation

The 1926 and 1927 age groups together consisted of 5336 men When the planned number of men had been screened we found fewer subjects with DBP ≥115 mmHg than expected An additional number of men born in 1927 were therefore screened Altogether 59 7% (n=3205) of the two age groups (50% and 70 2% respectively) were invited to the screening 74 1% (n=2376) of the invited subjects attended A total number of 107 (4 5%) subjects were on antihypertensive treatment 179 fulfilled the selection criteria but 36 of them were on antihypertensive treatment and were therefore not included in the study Another 8 were excluded because of diseases (valvular heart disease 4 previous myocardial infarction 1 previous stroke 1 chronic glomerulonephritis 1 and severe chronic alcoholism 1) and 15 subjects refused to participate in further investigations The remaining 120 subjects took part in the investigation They comprised 88 9% (120/135) of those who were eligible for the study In addition to the renal function studies an investigation of heart function and metabolic and hormonal variables was performed and will be reported separately

METHODS

The investigations took place at Sahlgren s Hospital Screening was performed in 1975 and 1976 from March to May and from Sept to Nov between 4 30 and 7 00 p m The renal function tests were carried out within one month of screening and were followed by a diagnostic work up at the Hypertension Clinic The subjects were on unrestricted diet and were treated as out patients throughout the study

Blood pressure

BP was measured in four different situations The arithmetic mean of the BP recordings in each situation was used DBP was recorded at phase five Mean arterial BP (MAP) was calculated as DBP+⅓ of the pulse pressure The rubber cuff used at screening was 12×30 cm and that used in the other three situations 12×35 cm

Casual BP At screening BP was measured once in the right arm with the subject in the seated position after a few minutes rest with a mercury manometer by the auscultation method BP was determined to the nearest 2 mmHg in order to avoid digital preference

BP during the clearance procedure determined to the nearest 1 mmHg was measured in the right arm with the subject in a semirecumbent position with an automatic device for cuff inflation and deflation with simultaneous registration of cuff pressure Korotkoff sounds and ECG (44) During the clearance periods BP was registered twice every 10 min altogether 18 times during two hours The mean of these BP values was used

BP after rest was measured twice after the subjects had been resting recumbent for 45 minutes in a sound protected room The same technique as at the clearance investigation was used

BP at the Out Patient Hypertension Clinic was measured on three different occasions within one month of the renal function studies BP was registered after 5 min supine rest using the same method as at screening

Heart rate

At screening and at the Hypertension Clinic heart rate was determined by pulse palpation In the clearance periods and after 45 min of rest it was calculated from the BP recordings

Height and weight

The method of Rose and Blackburn (36) was applied in these measurements Body surface area (BSA m²) was calculated according to Isaksson s method (27)

$$1+\frac{\text{height (cm)}-160+\text{weight (kg)}}{100}$$

Clearance

GFR was measured as inulin clearance (Cl_{in}) and *renal plasma flow* as p-aminohippurate clearance (Cl_{PAH}) using the continuous infusion technique Extraction of PAH was not measured The clearance measurements were performed between 8 and 11 a m After a priming dose of 4[?] ml of 25% inulin (Inutest Laevosan) and 20 ml of 20% PAH (Sodium Aminohippurate MSD) dissolved in 100 ml of saline (0 9%) a constant infusion was given aiming at a plasma concentration of 20 mg/100 ml for inulin and 2 mg/100 ml for PAH After an equilibrium period of 45 min three consecutive 40-minute clearance periods were studied The subjects were hydrated with 10 ml of water/kg b wt before the clearance measurements and water was then given to compensate for diuresis The diuresis was 8 2±3 7 ml/min (mean ± S D) during the three clearance periods Urine was collected without catheterization A plastic cannula was inserted into a cubital vein in each

arm. The infusion was given in the left arm and blood samples were taken from the right arm in the middle of each period. Inulin was analyzed according to the method of Hubbard and Loomis (25) and PAH according to the method of Brun (13). The errors of inulin and PAH measurement were checked in a series of 20 consecutive samples which were analyzed twice. The difference between the first and second determination was not significant. The error of a single determination, expressed as per cent of the mean, was 4.5% for u-inulin, 9.1% for p-inulin, 5.6% for u-PAH and 5.0% for p-PAH. The values of Cl_{in} and Cl_{PAH} were corrected for 1.73 m² BSA. Clearance measurements were successfully performed in 111 of the 120 subjects. The reason for failure was difficulty in voiding in 8 cases and a pronounced vasovagal reaction in one case. Owing to voiding difficulties and technical problems, 13 of the 111 men were subjected to the test a second time within one month.

Endogenous creatinine clearance (Cl_{cr}) was determined from the 24-hour urinary creatinine excretion rate and the plasma creatinine concentration. Urine was collected by the subjects for three consecutive 24 hour periods after giving them detailed instructions. Blood for p-creatinine was drawn in the morning after the last 24-hour urinary collection had been completed. Creatinine was determined by Autoanalyser at the Department of Clinical Chemistry. The mean Cl_{cr} of the three 24-hour periods was used. The value was corrected to 1.73 m² BSA.

Filtration fraction was calculated as the Cl_{in}/Cl_{PAH} ratio.

Haematocrit (Hct) was measured after centrifugation of blood in a Hct centrifuge (Kemila, Sweden).

Renal blood flow was calculated as $Cl_{PAH}/1-Hct$ (38).

Renal vascular resistance (RVR) was calculated as

$$\frac{\text{MAP during clearance}}{\text{RBF}}\left(\frac{\text{mmHg}\times\text{min}}{\text{l}}=\frac{80.0\ \text{dynes}\times\text{s}}{\text{cm}^5}=\frac{8.0\times10^6\ \text{Pascal}\times\text{s}}{\text{m}^3}\right)$$

Renal concentrating capacity was measured using the vasopressin test (Pitressin tannate in oil, Parke Davis) according to the method of de Wardener (42).

Diagnostic work up

A detailed history was recorded and a physical examination was performed at the Hypertension Clinic. The ocular fundi were examined. A chest X-ray was taken and the serum concentrations of sodium, potassium, calcium, creatinine, urate and plasma aldosterone were measured. Urine tests for glucose, sediment and bacterial culture were also performed. The 24-hour urinary excretion of albumin, catecholamines and cortisol was determined. Isotope renography was performed using standard methods and equipment (2). In patients with abnormal radiorenograms, further investigation was performed by i.v. pyelography or renal aortography.

Characteristics of the study population ($n=111$)

Three clinical groups were defined mainly to make comparisons with other studies possible. Subjects with a DBP of ≥105 mmHg (mean of three BP measurements) at the Out Patient Hypertension Clinic were regarded as hypertensives ($n=23$). Subjects with a screening DBP of <95 mmHg and a DBP of ≤ 90 mmHg (mean of three recordings) at the Hypertension Clinic constituted the normotensive group ($n=20$) and the remaining subjects were allocated to the borderline group ($n=68$).

Height, weight and BSA in the three groups are shown in Table II. Both the borderline subjects and the hypertensives were significantly heavier than the normotensives and had a larger BSA. Mean weight was 10.4 kg higher in the hypertension than in the normotension group.

The prevalence of cardiac enlargement (≥500 ml/m² BSA), left ventricular hypertrophy on the ECG, elevated s-creatinine and increased urinary albumin excretion is shown in Table III. In the hypertension group three of the subjects with cardiac enlargement on X-ray also had left ventricular hypertrophy on ECG. Heart size was calculated according to the method of Jonsell (28). Left ventricular hypertrophy on the ECG was diagnosed according to the Minnesota Code (3.1 or 3.3 plus 4.1–3 or 5.1–3), i.e. a combination of amplitude and ST or T criteria was used (36).

Fundoscopic changes were all of grade I–II. None of the subjects had a history of or showed signs of myocardial infarction, angina pectoris, cardiac decompensation, intermittent claudication, stroke or diabetes mellitus. Abnormal renal findings were seen in only 4 subjects. One non-hypertensive subject had unilateral kidney aplasia with contralateral kidney hypertrophy (16×7.5 cm). His Cl_{in} was 101 and Cl_{PAH} 574 ml/min. Two hypertensive subjects had slight proteinuria (<1 g/24 h), but no haematuria. They had a GFR of 98 and 80 ml/min, respectively, and had no history of chronic glomerulonephritis. Another hypertensive subject with constant microscopic haematuria had chronic prostatitis diagnosed by cystoscopy. He had no proteinuria and his Cl_{in} was 95 and Cl_{PAH} 602 ml/min. All three hypertensives had normal pyelography findings.

Statistical methods

Standard methods were used for calculation of means, S.D., variation coefficients and correlation coefficients. The hypothesis of no difference in means between two groups was tested by Student's *t*-test. Only two-sided tests were used. The hypothesis of non-linear correlation between two variables was tested using the correlation coefficient. Values of $p<0.05$ were regarded as statistically significant.

In addition, the "sliding mean value" method (14) was used to describe the relationship between mean arterial BP during the clearance measurements and the renal function variables in the following way. The subjects studied were ranked from 1 to 111 by increasing BP and then subgrouped. The first subgroup comprised subjects with the lowest BP (nos. 1–40). The next subgroup comprised subjects 2–41, the third subjects 3–42, and so on. The mean value of BP and the mean value of the studied variable were plotted for each subgroup. The points were then joined to form continuous curves. The mean values varied very gradually since one subgroup differed from the next by only two subjects. Two extra subgroups, comprising

Table II *Systolic and diastolic BP (SBP DBP) mean arterial blood pressure (MAP) and heart rate (H) in four different situations and height weight and body surface area (BSA) in the clinical groups (mean S D)*

	Normotension group (*a*) (*n*=20)	Borderline group (*b*) (*n*=68)	Hypertension group (*c*) (*n*=23)	*t* tests for *a b c* (*p*<) *a b*	*a c*	*b c*
At screening						
SBP	130±11	162±14	189±16	0 001	0 001	0 001
DBP	84± 7	113±10	128±12	0 001	0 001	0 001
MAP	99± 8	130±11	148±12	0 001	0 001	0 001
HR	76±14	82±13	86±12	n s	0 025	n s
At the Hypertension Clinic						
SBP	127± 7	146±11	176±16	0 001	0 001	0 001
DBP	76± 6	93± 8	115± 7	0 001	0 001	0 001
MAP	93± 5	111± 9	135± 9	0 001	0 001	0 001
HR	70±11	74± 9	77±13	n s	n s	n s
During clearance measurements						
SBP	115±12	134±13	162±24	0 001	0 001	0 001
DBP	70± 7	86± 9	103±15	0 001	0 001	0 001
MAP	85± 7	101±10	123±17	0 001	0 001	0 001
HR	64±10	70±11	73±11	0 05	0 01	n s
After 45 min rest in a sound protected room						
SBP	112±11	132±13	158±24	0 001	0 001	0 001
DBP	63± 9	80±11	97±13	0 001	0 001	0 001
MAP	80± 8	97±11	117±16	0 001	0 001	0 001
HR	62±10	67±11	69± 8	n s	n s	n s
Height (cm)	176 4±5 2	177 0± 7 0	176 2± 7 0	n s	n s	n s
Weight (kg)	75 2±8 7	82 6±12 2	85 6±13 8	0 005	0 01	n s
BSA (m²)	1 92±0 11	2 00± 0 17	2 02± 0 18	0 02	0 05	n s

subjects 1–20 and 92–111 were formed in order to study the extreme values These curves thus describe how the mean value of a variable on the *y* axis changes when BP on the *x* axis increases The correlation between the variables studied is not demonstrated by these curves and is expressed in the usual way i e by the correlation coefficient and the regression equation The calculations were made by a computer (IBM 360/65) or a desk computer (P 652 Olivetti)

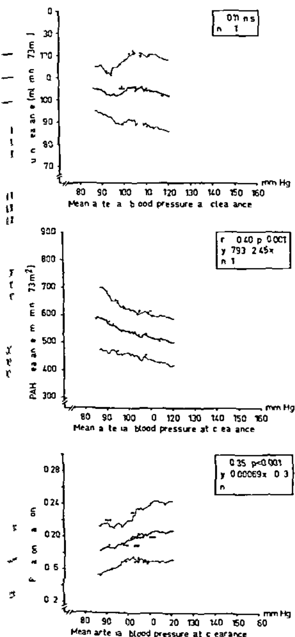
RESULTS

Blood pressure and heart rate

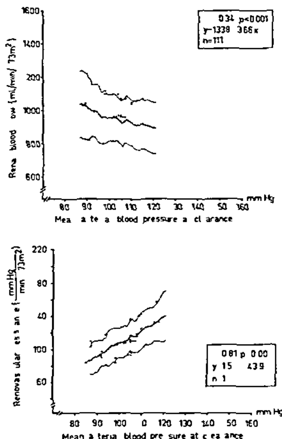
Table II gives the BPs and heart rates in the fou different situations for the three clinical groups The values were significantly higher at screenin than at the Hypertension Clinic except for SBP an heart rate in the normotension group Of the 6

Table III *Prevalence of cardiac enlargement ECG abnormalities elevation of s creatinine and urinar albumin excretion in the three clinical groups*

	Normotension group (*n*=20) *n*	%	Borderline group (*n*=68) *n*	%	Hypertension group (*n*=23) *n*	%
Cardiac enlargement on X ray (>500 ml/m² BSA)	1	5 0	3	4 4	4	17 4
Left ventricular hypertrophy on ECG	0	0	4	5 9	6	26 1
S-creatinine >114 μmol/l (>1 3 mg/100 ml)	0	0	0	0	0	0
U albumin >200 mg/24 h	0	0	2	2 9	4	17 4



F g 1 Mean values (th ck l nes) and S D (th n l nes) for Cl_{In}, Cl_{PAH} and FF in the success e BP groups The dashed l nes connect the means of the small groups (*n* 20) w th the lowest and h ghest BP w h the nearest group of 40 subjects The result of l near regress on analys s s also given



F g 2 Mean values and S D for RBF and RVR n the success ve BP groups For explanat on of the f gure see text to F g 1

subjects hav ng a DBP ≥115 mmHg at screen ng only 22 (32 8 %) were hypertensive accord ng to our arb trary def n t on BP during the clearance periods was almost as low as after 45 m n rest in the sound protected room wh ch ind cates that the clearance measurements were performed under almost basal cond tions

In l n clearance

Cl_{In} d d not increase sign f cantly with ncreas ng BP (*r* 0 11) (Fig 1) There was no s gn f cant d fference in Cl_{In} between the three cl n cal groups (Table IV)

Endogeno s creat n ne clearance

Cl_{cr} d d not change s gnif cantly w th increas ng BP (*r* 0 16) and d d not differ between the three clini cal groups (Table IV) The S D of Cl_{cr} const tuted 21 25 % of the mean value and that of Cl_{In} 10–14 % in the three cl nical groups The mean Cl_{cr}/Cl_{In} rat o was 1 3

PAH clearance

Cl_{PAH} decreased signif cantly with increas ng BP ($r = 0.40$ $p<0.001$) (F g 1) The decrease was

Table IV *Inulin clearance (Cl_{in}) endogenous creatinine clearance (Cl_{cr}) PAH clerance (Cl_{PAH}) filtration fraction (FF) haematocrit (Hct) renal blood flow (RBF) renovascular resistance (RVR) and urina concentration test in the normotension borderline and hypertension groups (mean ± S D)*

Cl_{in} Cl_{cr} Cl_{PAH} RBF and RVR are corrected to 1 73 m² BSA

	Normotension group (*a*) (*n*=20)	Borderline group (*b*) (*n*=68)	Hypertension group (*c*) (*n*=23)	*t* tests for *a b c* (*p*<)		
				a b	*a c*	*b c*
Cl_{in} (ml/min)	108 8±10 5	103 3±13 9	102 2±14 2	n s	n s	n s
Cl_{c} (ml/min)	133 9±28 6	131 3±30 2	128 2±31 9	n s	n s	n s
Cl_{PAH} (ml/min)	616±123	532±87	505±91	0 01	0 005	n s
FF	0 184±0 035	0 197±0 031	0 207±0 029	n s	0 05	n s
Hct (%)	42 8±1 9	43 5±2 1	44 7±2 2	n s	0 005	0 05
RBF (ml/min)	1 088±221	942±152	911±150	0 02	0 005	n s
RVR (mmHg/l/min)	82 0±17	111 2±23	139 8±36	0 001	0 001	0 005
Urinary concentration test (mOsm/kg H_2O)	995±118	979±107	974±130	n s	n s	n s

gradual and continuous Cl_{PAH} was also significantly lower in the borderline and hypertension groups than in the normotension group but there was no significant difference between the borderline and hypertension groups (Table IV)

Filtration fraction

FF increased significantly and linearly with increasing MAP (r=0 35 p<0 001) (Fig 1) FF was significantly higher in the hypertensive than in the normotensive group but there was no significant difference in FF between the borderline group and the other groups

Haematocrit

Hct increased significantly with increasing MAP (r=0 37 p<0 001) Hct was significantly increased in the hypertension group compared with the other two groups but there was no significant difference in Hct between the normotension and the borderline group (Table IV)

Renal blood flow and renovascular resistance

As anticipated from the Cl_{PAH} curve in Fig 1 RBF decreased significantly with increasing BP (r=−0 34 p<0 001) (Fig 2) The decrease was continuous and started in the lowest BP range The decrease with increasing BP in RBF was less steep than in Cl_{PAH} owing to the increase in Hct with increasing MAP RBF was significantly lower in the borderline and hypertension groups than in the normotension group but there was no significant difference in RBF between the borderline and the hypertension groups (Table IV) The finding that RBF decreased with increasing BP means that RV increased drastically with increasing BP (r=0 8 p<0 001) The relationship seems to be linear Th difference in RVR between any two of the clinic groups was also significant (Table IV)

Renal concentrating capacity

Urine osmolality in the whole study group did n change significantly with increasing BP (r=0 01 but there was a tendency towards higher conce trating capacity in the lowest limits of the BP ran (Fig 3) There was no significant difference in urir osmolality between the three clinical groups (Ta ble IV)

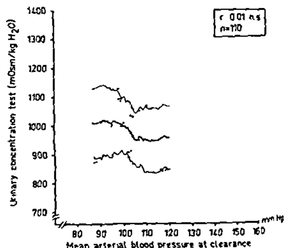


Fig 3 Mean values and S D for maximal urinary concentrating capacity in the successive BP groups For explanation of the figure see text to Fig 1

DISCUSSION

This study of renal haemodynamics and renal function in essential hypertension was performed in a nonselected population sample of untreated 49 year old men The results are not influenced by variations due to age sex or treatment which is important since RBF GFR and renal concentrating capacity are known to decrease with age (17 34) and may be lower in women than in men (38 43) and since antihypertensive treatment even after withdrawal for several weeks (3) is known to influence many of the variables studied (18 26 35)

An enrichment of subjects in the upper part of the BP range was performed in order to obtain a sufficient number of subjects to ensure a correct description of factors related to BP in the borderline and definitely hypertensive part of the BP distribution *The criteria for inclusion should have ensured* that these subjects were representative for all BP levels Thus the analysis provides an opportunity to determine at what BP level and in what sequence various functional changes appear

Although BP is roughly normally distributed in the population—which means that there are no fixed limits for normotension borderline or definite hypertension—three such groups were defined to allow comparison with other studies and to give absolute values for these groups mainly defined according to clinical criteria established in Sweden (8) However it is difficult to compare the absolute values in this study with those in some other studies of renal function in selected groups with varying age sex and severity of hypertension This is exemplified by a recent cross sectional study in which renal function in hypertensives was related to age in order to study the changes in renal function in relation to the duration and development of hypertension (29) 207 subjects with BP higher than 150/100 mmHg (age range 17–63 years) were studied An increase in BP and a decrease in GFR and renal plasma flow with increasing age were found Renal plasma flow decreased more steeply with age in these hypertensives than in normal subjects in various other studies but it is difficult to determine how much of the observed changes were caused by aging and how much by hypertension

The finding in our study that GFR did not differ significantly between normotensives and untreated hypertensives is in accordance with the results of an earlier study of a random sample of middle aged men in whom GFR was measured by a single injection technique (7) In that study GFR was 100 ml/min in normotensives and 96 ml/min in hypertensives These values are slightly lower than those found by us but the single injection technique gives slightly lower GFR than inulin clearance (12)

The decrease in RBF with increasing BP may be an effect of both the severity and the duration of elevated BP The steeper decrease in renal plasma flow than in RBF was due to an increase in Hct with increasing BP Higher Hct values in hypertensives than in normotensives have previously been reported in a random population sample (40) The absolute values of RBF are underestimated as no correction for PAH extraction was made According to Smith (38) the PAH extraction is about 0 90 in normal subjects and it is not substantially reduced until Cl_{PAH} is less than 300 ml/min As no *subject in the study had a renal blood flow of less* than 300 ml/min or abnormally low GFR it is likely that the PAH extraction was the same at all BP levels

The decrease in RBF with increasing BP may be explained by increased sympathetic discharge to the kidneys and/or the action of circulating vasoconstrictors The renal sympathetic activity recorded from single fibres is reported to be twice as high in spontaneously hypertensive than normotensive rats (41) The question whether there is an increased activity of the sympathetic nervous system in essential hypertension has not been settled (4 32 37) The response to both low doses of noradrenaline and angiotensin II closely mirrors the haemodynamic pattern seen in this study including largely unchanged GFR decreased RBF and increased FF (1 21 22) The decrease in RBF can also be explained by structural changes in the renal resistance vessels in the form of an increased media thickness leading to an increased wall/lumen ratio Such changes have been shown to give rise to an exaggerated resistance response of the renal vascular bed to graded doses of noradrenaline in spontaneously hypertensive rats compared with normotensive controls although the sensitivity to threshold doses of noradrenaline was the same in the two types of rats (19)

Thus the study has shown that the primary feature in the early stages of essential hypertension is an adjustment of renal haemodynamics so that the glomerular filtration is kept constant The adjustment is accompanied by an increase in FF This

indicates an increased efferent to afferent arteriolar resistance The filtration pressure in the glomerular capillary will thereby be maintained or even slightly increased Direct measurements with micropuncture technique have shown higher glomerular capillary pressures in certain strains of hypertensive rats than in controls (5)

GFR is also determined by the area and the permeability of the glomerular capillary There is no evidence that an increase of the area would be present in early hypertension A positive correlation has been found between BP and urinary albumin excretion both in normotension and hypertension (33) indicating a significant influence of the BP on the permeability of the glomerular capillary for macromolecules It has been suggested that the permeability of the glomerular capillary may be decreased in hypertension owing to a genetic defect (10) This defect would be compensated by an increase in the filtration pressure

The intrarenal pressure may also influence the filtration pressure and hence the GFR Lowenstein et al (31) observed an increase in intrarenal pressure in hypertensive subjects compared to normotensives but this could not be reproduced by Willassen and Ofstad (45) If the intrarenal pressure would be elevated it would tend to decrease GFR which is not consistent with our findings The available evidence thus indicates that the net filtration pressure is slightly increased in early hypertension maintaining the GFR despite the decrease in RBF

The renal concentrating capacity was not significantly correlated to the BP levels in our subjects all of whom had normal or slightly reduced GFR We therefore find it highly improbable that the concentrating capacity is reduced early in the hypertensive disease as has been claimed (30)

From this study in an epidemiologically defined population based on 111 persons we conclude that renal function in early stages of essential hypertension is characterized by 1) Increased renovascular resistance and decreased RBF These haemodynamic changes do not start at any particular BP level 2) Unchanged GFR accompanied by an increase in FF Thus an autoregulation of GFR was demonstrated at all BP levels studied The evidence suggests that GFR is maintained by an increase in glomerular capillary pressure 3) Unchanged maximal renal concentrating capacity

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REFERENCES

1 Aurell M Renal response in man to plasma volu expansion and angiotensin Scand J Clin Lab Inv (Suppl) 112 1969
2 Aurell M Jonsson S & Nilsson S On the qua tation of radiorenograms Scand J Clin Lab Inv 28 291 1971
3 Aurell M Pettersson M & Berglund G Ren angiotensin system in essential hypertension Lan 2 342 1975
4 Axelrod J Review Catecholamines and hypert sion Clin Sci Mol Med 51 415 1976
5 Azar S Tobian L & Johnson M A Glomerul efferent arteriolar peritubular capillary and tubu pressures in hypertension Am J Physiol 227 10 1974
6 Bello C T Sevy R W Ohler E A Papacost C A & Bucher R M Renal hemodynamic sponses to stress in normotensive and hypertens subjects Circulation 22 573 1960
7 Berglund G Aurell M & Wilhelmsen L Re function in normo and hypertensive 50-year males Acta Med Scand 199 25 1976
8 Berglund G Isacsson S O & Rydén L T Skaraborg project a controlled trial regarding the fect of structured hypertension care Acta Med Sca (Suppl) 626 64 1979
9 Berglund G & Wilhelmsen L Factors related blood pressure in a general population sample Swedish men Acta Med Scand 198 291 1975
10 Bianchi G Gatti M Ferrari P Picotti G E Colombo G Velis O Cusi D Lupi G P Bark sina C Bracchi G Gori D & Mazzei D A ren abnormality as a possible cause of essential hype tension Lancet I 173 1979
11 Birkenhäger W H & Schalekamp M A D H Control mechanisms in essential hypertension p 4 Elsevier Scientific Publ Co Amsterdam Oxford an New York 1976
12 Brochner Mortensen J & Rødbro P Selection o routine method for determination of glomerular filtra tion rate in adult patients Scand J Clin Lab Inves 36 35 1976
13 Brun C A rapid method for the determination o para aminohippuric acid in kidney function tests Lab Clin Med 37 955 1951
14 Chau N P Safar M E Weiss Y A London G M Simon A C & Milliez P L Relationship between cardiac output heart rate and blood volume in essential hypertension Clin Sci Mol Med 54 1 1978
15 Corcoran A C & Page I H Quantitative formu

tion of maximum urinary specific gravity J Mt Sinai Hosp 8 459 1942
16 Corcoran A C Taylor R D & Page I H Functional patterns in renal disease Ann Intern Med 28 560 1948
17 Davies D F & Shock N W Age changes in glomerular filtration rate effective renal plasma flow and tubular excretory capacity in adult males J Clin Invest 29 496 1950
18 Falch D K Ødegaard A E & Norman N Renal plasma flow and cardiac output during hydralazine and propranolol treatment in essential hypertension Scand J Clin Lab Invest 38 143 1978
19 Folkow B Hallback M Lundgren Y & Weiss L Renal vascular resistance in spontaneously hypertensive rats Acta Physiol Scand 83 96 1971
20 Goldring W & Chasis H Hypertension and hypertensive disease p 82 Commonwealth Fund New York 1944
21 Gombos E A Hulet W H Bopp P Goldring W Baldwin D S & Chasis H Reactivity of renal and systemic circulations to vasoconstrictor agents in normotensive and hypertensive subjects J Clin Invest 41 203 1962
22 Hall J E Guyton A C Salgado H C McCaa R E & Williamson Balfe J Renal hemodynamics in acute and chronic angiotensin II hypertension Am J Physiol 235(3) F174 1978
23 Hilden T Diodrast clearance in essential hypertension Acta Med Scand (Suppl) 206 242 1948
24 Hollenberg N K Adams D F Solomon H Chenitz W R Burger B M Abrams H L & Merill J P Renal vascular tone in essential and secondary hypertension Hemodynamic and angiographic responses to vasodilators Medicine 54 29 1975
25 Hubbard R S & Loomis T A The determination of inulin J Biol Chem 145 641 1942
26 Ibsen H & Sederberg Olsen P Changes in glomerular filtration rate during long term treatment with propranolol in patients with arterial hypertension Clin Sci 44 129 1973
27 Isaksson B A simple formula for the mental arithmetic of the human body surface area Scand J Clin Lab Invest 10 283 1958
28 Jonsell S A method for determination of heart size by teleroentgenography (a heart volume index) Acta Radiol 20 325 1939
29 de Leeuw P W Kho T L Falke H E Birkenhager W H & Wester A Haemodynamic and endocrinological profile of essential hypertension Acta Med Scand (Suppl) 622 1979
30 de Leon Jr A C Dreifus L S & Bellet S Urinary osmolar concentration A means of evaluating early renal function changes in essential hypertension Am J Med Sci 239 144 1960
31 Lowenstein J Beranbaum E R Chasis H & Baldwin D S Intrarenal pressure and exaggerated natriuresis in essential hypertension Clin Sci 38 359 1970
32 Mendlowitz M & Vlachakis N D The catecholamines in essential hypertension Am Heart J 91 378 1976
33 Parving H H Mogensen C E Jensen H Æ & Evrin P E Increased urinary albumin excretion rate in benign essential hypertension Lancet 1 1190 1974
34 Rapoport A Husdan H Wilkins G E & Gryfe C I A standardized test of renal concentrating capacity in adults with some results in essential hypertension Can Med Assoc J 101 741 1969
35 Reubi F C The late effects of hypotensive drug therapy on renal functions of patients with essential hypertension In Essential hypertension An international symposium Bern 1960 (ed K D Boch and P T Cottier) p 317 Springer Verlag Berlin 1960
36 Rose G A & Blackburn H Cardiovascular survey methods WHO Monogr Ser 56 1968
37 Sever P S Catecholamines in essential hypertension the present controversy In Circulating catecholamines and blood pressure (ed W H Birkenhager and H E Falke) p 1 Bunge Scientific Publications Utrecht 1978
38 Smith H W The kidney Structure and function in health and disease pp 164 550 Oxford University Press New York 1951
39 Smith H W Goldring W Chasis H & Ranges H A Observations on the effective renal blood flow and functional excretory mass in man with special reference to essential hypertension Am J Physiol 123 189 1938
40 Tibblin G Bergentz S E Bjure J & Wilhelmsen L Hematocrit plasma protein plasma volume and viscosity in early hypertensive disease Am Heart J 72 165 1966
41 Thorén P & Ricksten S E Recordings of renal and splanchnic sympathetic nervous activity in normotensive and spontaneously hypertensive rats Clin Sci Mol Med 57 197 1979
42 de Wardener H E Vasopressin tannate in oil and the urine concentration test Lancet 1 1037 1956
43 Wesson L G Physiology of the human kidney p 96 Grune & Stratton New York 1969
44 Wikstrand J Berglund G Wilhelmsen L & Wallentin I Orthogonal electrocardiogram apex cardiogram and atrial sound in normotensive and hypertensive 50-year-old men Br Heart J 38 779 1976
45 Willassen Y & Ofstad J Intrarenal pressure and sodium excretion in essential hypertension In The Marstrand hypertension meeting 1976 Acta Med Scand (Suppl) 602 88 1977

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The Effects of Cimetidine (Tagamet®) on Renal Function in Patients with Renal Failure

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ABSTRACT Cimetidine has been administered during 7 days to 28 patients with different degrees of renal failure Thirteen of these patients had a further week's treatment at least one month later The daily dose of cimetidine was reduced in relation to pretrial values of creatinine clearance There was a clear rise in serum creatinine all through the trial (22 3±2 6% at day 7) ($p<0\ 001$) Maximal decreases in creatinine clearance occurred on day 2 (21 8±2 2%) and day 3 (23±2 0%) ($p<0\ 001$), but were still present on days 6 (16 4±2 9%) and 7 (17.3±2 8%) ($p<0\ 001$) There was a small rise in serum uric acid all through the trial ($p<0\ 05$) Three days after finished treatment there were no significant differences in serum creatinine, creatinine clearance and serum uric acid when compared to pretrial values The pattern of changes in serum creatinine and creatinine clearance was the same in both mild and severe renal failure Glomerular filtration rate determined by [[1]Cr] EDTA clearance before, on day 3 of treatment and 3 days after treatment did not show any differences No change was seen in serum β_2-microglobulin during the trial The decrease in creatinine clearance during treatment with cimetidine is probably not caused by a reduction of glomerular filtration rate, but could be explained by competition by cimetidine for tubular secretion of creatinine Treatment with cimetidine of patients with renal failure may invalidate measurements of serum creatinine and creatinine clearance as standard routine tests for glomerular filtration rate

Key words cimetidine renal function renal failure inhibited tubular secretion creatinine uric acid
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In patients with peptic ulcer disease and normal serum creatinine there is a small but significant increase in serum creatinine usually within normal limits during the first weeks of treatment with cimetidine (3 4 16 20) Values return to pretreatment levels during continued long term treatment (4) A decrease in creatinine clearance has been reported already after single oral or i v doses of cimetidine in healthy man but inulin clearance remained constant (10 14) and creatinine clearance normalized at the end of one week s treatment in high doses (10) In patients with peptic ulcer disease and normal renal function both creatinine and [[51]Cr]EDTA clearances were decreased after one day of treatment with cimetidine 1 6 g/d (15) These decreases were also accompanied by a decrease in effective renal plasma flow determined with [[125]I]hippuran clearance (15) After 3 and at the end of 12 weeks treatment with cimetidine in the same doses the clearance values for creatinine [[51]Cr]EDTA and [[125]I]hippuran had returned to the pretreatment values (15) We have previously reported significant increases within normal limits in serum creatinine and serum β_2 microglobulin after 2 and 6 weeks treatment with cimetidine 1 0 g/d in patients with peptic ulcer disease and normal serum creatinine (20) However [[51]Cr]EDTA and creatinine clearances were unchanged during treatment compared to pretreatment values (20) Cimetidine has been shown to be effective in the prophylactic treatment of upper gastrointestinal haemorrhage in renal transplant recipients (18) and could be of value in patients on regular haemodialysis (12 17) Nothing is known however about the effect of cimetidine on renal function in patients with established renal failure

The aim of this study was to investigate the effect on renal function in patients with renal failure during treatment with cimetidine for one week The doses were adjusted to the degree of renal failure according to the results of a previous oral single dose study (21)

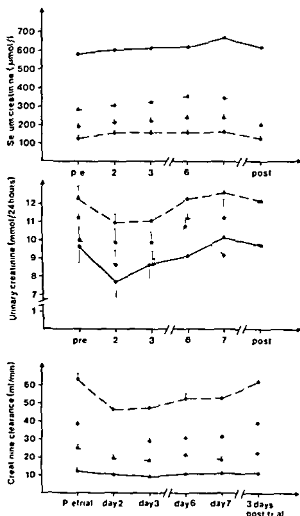


Fig 1 Serum creatinine 24-hour urinary creatinine and creatinine clearance (mean ± S E) before during and after cimetidine treatment for 7 days in patients with a creatinine clearance of 5–15 ml/min (—) (5 treatment periods) 15–30 ml/min (—) (10 treatment periods) 30–50 ml/min ( ) (13 treatment periods) and 50–75 ml/min (– –) (13 treatment periods) $^*p<0.05$ $^{**}p<0.01$ compared to pretrial values (Wilcoxon s test for paired differences)

PATIENTS AND METHODS

Twenty-eight outpatients 8 women and 20 men mean age 56 years (range 29–77) with different degrees of renal failure were treated with cimetidine for 7 days In 13 patients the investigation was repeated at least one month after the first investigation making a total of 41 treatment periods Nine patients had glomerulonephritis 9 nephroarteriosclerosis 3 pyelonephritis 3 interstitial nephropathy 3 polycystic kidney disease and 1 patient diabetic nephropathy They did not have apparent gastrointestinal disease and the renal function had been stable for a minimum of one month before the trial All patients received their usual drug treatment during the trial including antihypertensives diuretics chemotherapeutics allopurinol and antacids Even irregular intake of ant[illegible] before and during the trial was recorded All gave [illegible] informed consent before entering the trial

The doses of cimetidine were adjusted in relation t[illegible] creatinine clearance values determined within a wee[illegible] fore trial as follows Cimetidine 200 mg 2 times daily [illegible] given to 5 patients with a creatinine clearance of [illegible] ml/min (5 treatment periods) 200 mg 3 times daily [illegible] patients with a creatinine clearance of 15–30 ml/mi[illegible] treatment periods) 200 mg 4 times daily to 8 patients [illegible] a creatinine clearance of 30–50 ml/min (13 treat[illegible] periods) and 200 mg 3 times daily and 400 mg at bedti[illegible] 9 patients with a creatinine clearance of 50–75 ml/m[illegible] treatment periods)

Creatinine urea uric acid phosphate calcium β_2-microglobulin in serum and endogenous 24-[illegible] creatinine clearance were estimated in duplicate d[illegible] the week before entry to the trial on days 2 3 6 an[illegible] treatment and 3 days after treatment In 15 patients [illegible] moderate degree of renal failure [^{51}Cr]EDTA clea[illegible] with a simplified single injection technique (5) was d[illegible] mined 2 days before on day 3 during and 3 days [illegible] treatment Blood samples were drawn at 180 200 22[illegible] 240 min after i v injection of 100 µCi [^{51}Cr]EDT[illegible] The clearance values of creatinine and [^{51}Cr]EDTA [illegible] corrected to 1 73 m² BSA Serum β_2 microglobulin [illegible] analyzed by a radioimmunosorbent technique (Pha[illegible] β_2 microglobulin test Pharmacia Diagnostics Upp[illegible] Besides these laboratory investigations routine bloo[illegible] urine chemical analyses were performed during the t[illegible]

The statistical analyses were performed with Stud[illegible] paired *t* test and Wilcoxon s test for paired differe[illegible] The results are given as mean ± S E

RESULTS

The effect of cimetidine on serum and uri[illegible] creatinine and creatinine clearance in the 4 gr[illegible] of patients with renal failure during cimeti[illegible] treatment are given in Fig 1 Mean 24 hour uri[illegible] excretion of creatinine decreased significantly [illegible] days 2 and 3 except in patients with a creati[illegible] clearance of 5–15 ml/min During continued tr[illegible] ment urinary creatinine excretion returned to [illegible] trial levels on days 6 and 7 There were statistic[illegible] significant increases in serum creatinine and [illegible] creases in creatinine clearance in all groups of [illegible] tients with renal failure except again for the gr[illegible] with a creatinine clearance of 5–15 ml/min All [illegible] ues returned to the pretrial values 3 days postt[illegible] The mean percentage increase in serum creatini[illegible] for all 41 treatment periods was more pronounc[illegible] on days 6 (21 8%) and 7 (22 3%) than on days [illegible] (13 8%) and 3 (16 3%) The mean percentage d[illegible] crease in creatinine clearance seemed to be mo[illegible] pronounced during days 2 (21 8%) and 3 (23 9[illegible] than during days 6 (16 4%) and 7 (17 3%)

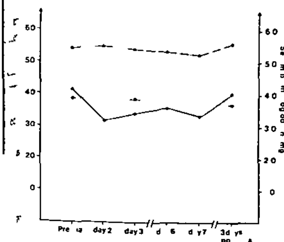
Table I *Ur c ac d calc n and pl spl ate n ser n i 22 pat ents tl renal fa l re before d r ng and after 33 treatment per ods tl c met d ne for 7 da s (n ean + S E range n parentl eses)*

T me n rela on to t eatment	Serum unc ac d (µmol/l)	Serum calc um (mmol l)	Serum phosphate (mmol l)
Before treatment	4_5+17 (255–644)	2 46+0 01 (2 29 2 68)	1 13+0 03 (0 70–1 71)
During trea ment			
Day 2	437+17	? 43+0 01	1 20+0 03
Day 3	438+16	? 40+0 01**	1 19+0 04
Day 6	446+17**	2 41+0 01**	1 10+0 04
Day 7	447+18	2 41+0 01**	1 16+0 04
3 days after treatment	4 5+17	? 40+0 01**	1 14+0 04

$p<0.05$ $^{**}p<0.01$ $^{***}p<0.001$ compared to resul s before t ea ment (S udent s pa red t tes)

The 15 pat ents with a moderate degree of renal fa lure in whom [Cr]EDTA clearance was meas ured had a mean pretrial creatin ne clearance of 11 3 ml/m n and a mean [Cr]EDTA clearance of 37 3 ml/m n (F g ?) Mean creat n ne clearance decreased s gn f cantly during treatment and returned to the pretrial value 3 days after treatment Mean [Cr]EDTA clearance on day 3 during treatment and 3 days after treatment was unchanged Mean serum β m croglobul n concentrat on was unchanged during the trial (F g 2)

Uric ac d calc um and phosphate n serum were analyzed during 33 treatment periods n 2? patients Table I) The mean value of serum uric acid before



F g 2 Serum β_2 m croglobul n ( ) 24-hour creat ne clearance (—) and [Cr]EDTA clearance (---) during and after treatment w th c met d ne for 7 days (mean + S E) n 15 pat ents w h renal fa lure $p<0.05$ * $p<0.01$ compared to pre rial values (W l xon s test for paired d fferences)

treatment was 4?5 µmol/l and there were small but stat st cally s gn f cant ncreases of 2 8–6 1% from day ? to day 7 with a return to the pretrial mean value 3 days posttrial The accepted reference interval for serum uric acid is 140–340 µmol/l for women and ?00–4?0 µmol/l for men Mean serum calc um before treatment was 2 46 µmol/l (accepted reference interval 2 ?5–? 75) and decreased sl ghtly but significantly from day 3 throughout the trial Three days after treatment mean serum calcium had st ll not returned to the pretrial value Mean serum phosphate before the trial was 1 13 mmol/l (accepted reference nterval 0 6–1 6) There was a slight but stat st cally s gn f cant increase on day 2 during treatment w th a return to the pretrial value during cont nued treatment In 19 treatment periods in 16 pat ents not treated with antac ds there was also a statist cally s gn f cant increase in serum phosphate on day 3 during treatment ($p<0.01$) as well as on day 2 ($p<0.05$)

There were no s gn ficant changes in serum urea transam nases creatine phosphokinase and rou t ne blood or urine tests during the trial The pat ents had no side effects during the trial

DISCUSSION

In our pat ents w th d fferent degrees of renal fa lure treated with cimet d ne for one week mean urinary excretion of creat n ne decreased s gn ficantly on days 2 and 3 but returned to the pretrial value on days 6 and 7 during cont nued treatment Th s caused sign f cant increases in serum creat n ne and decreases in creat n ne clearance from day ? to day 7 during treatment The decreases in creat n ne clearance seemed to be more pronounced on days 2

and 3 compared to days 6 and 7 despite higher values of serum creatinine on days 6 and 7. This pattern may be interpreted in the following way: Reduction of urinary creatinine excretion causes accumulation of creatinine until a new steady state in which the daily amount of excreted creatinine matches the amount released by metabolism each day is achieved on days 6 and 7.

The pattern and degree of changes in serum creatinine were the same in mild, moderate and severe renal failure. This resulted in more pronounced increases in serum creatinine in patients with severe renal failure. Mean serum creatinine in patients with a creatinine clearance of 5–15 ml/min before treatment was 582 µmol/l and on day 7 671 µmol/l, while in patients with a creatinine clearance of 50–75 ml/min the corresponding means were 126 and 155 µmol/l, respectively (Fig. 1).

The rise of serum creatinine during cimetidine treatment could not be explained by an excessive increase in endogenous production of creatinine since creatine phosphokinase in this and other trials (10, 20) did not change. This is supported by the fact that there was no increase in the urinary excretion of creatinine. The increase in serum creatinine could not be attributed to interference of cimetidine or its sulphoxide metabolite on analysis of creatinine in serum (10).

[^{51}Cr]EDTA clearance, which is a highly specific method for the determination of glomerular filtration rate and has an excellent correlation to inulin clearance (6), was unchanged during this trial. Thus the changes in serum creatinine and creatinine clearance could not be explained by a reduction of glomerular filtration rate. The unchanged mean serum β_2-microglobulin during this trial supports the opinion that glomerular filtration rate is not influenced by cimetidine therapy in patients with renal failure.

Cimetidine is reported to be rapidly excreted via the kidneys mainly as unchanged drug (9). The mean renal clearance of cimetidine in normal man is 400–500 ml/min (19, 23), which means that about 2/3 is secreted in the tubules. Creatinine is mainly cleared by glomerular filtration but small quantities are also secreted and possibly also reabsorbed in the tubules (1, 24, 25). The tubular maximum for secretion of creatinine exceeds that of reabsorption, which explains why the creatinine clearance values in normal man are 5–10% higher than glomerular filtration rate determined by inulin clearance (13).

In renal failure, creatinine clearance may exceed inulin clearance by as much as 50–100% (13). The creatinine clearance/[^{51}Cr]EDTA clearance ratio before treatment in our patients was 1.11 and decreased by day 3 to 0.89. This might be explained by inhibited tubular secretion of creatinine caused by competition by cimetidine for the same tubular transport system. Reabsorption of creatinine therefore dominates over secretion.

Tubular secretion by active transport is effectuated through an acid or base secreting system (1). Weak acids such as carinamide (4-carboxy-phenyl-methan-sulfanilamide) (8) and salicylate (11) are known to decrease the tubular secretion of creatinine in man, thus proving that creatinine is secreted by the secretory system for weak acids. Berglund et al. (2) however reported that trimethoprim, which like cimetidine is a weak base, also inhibits the tubular secretion of creatinine. They concluded that creatinine secretion in man also might take place through the base transport system as well.

Mean serum uric acid in our patients was slightly above the accepted reference interval before treatment, as a result of renal failure and/or diuretic therapy. There was a small but significant increase in mean serum uric acid during treatment, with a return to the pretrial value after withdrawal of treatment. Like creatinine, uric acid follows a proximal secretion pattern, i.e. secretion takes place at a site proximal to reabsorption (1). Unlike creatinine, the tubular maximum for reabsorption exceeds that of secretion (1). Uricosuric drugs like sodium salicylate and probenecid increase the renal excretion of uric acid due to inhibited tubular reabsorption (22). However, in small doses these drugs have been reported to decrease the excretion of uric acid due to inhibition selectively of the tubular secretion without effect on tubular reabsorption (2). It thus seems possible that cimetidine, like salicylate, could compete with uric acid as well as creatinine for secretion in the tubules.

The slight changes in calcium and phosphate in serum observed in this study are difficult to explain but are probably not due to any primary effect of cimetidine on renal function.

In summary, treatment with cimetidine does not seem to cause any impairment of glomerular filtration rate in patients with renal failure. The observed increase in serum creatinine and decrease in creatinine clearance might be caused by inhibited

tubular secretion of creatinine which is reversed after withdrawal of treatment This may however be of clinical importance since cimetidine treatment may invalidate serum creatinine and creatinine clearance as standard routine tests of glomerular filtration rate This is especially important in renal transplant recipients during treatment with cimetidine in whom a rise of 15–20% in serum creatinine would make a transplant rejection suspect and might lead to an increase in immunosuppressive therapy Serum β microglobulin should perhaps be used as a complementary simple renal function test to monitor renal transplant function in patients treated with cimetidine Further renal function investigations are needed in patients with renal failure and peptic ulcer disease treated with cimetidine to evaluate whether the changes in serum creatinine and creatinine clearance are reversible during longer treatment periods as has been described in patients with normal renal function (4)

ACKNOWLEDGEMENTS

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REFERENCES

1 Berglund F Urinary excretion patterns for substances with simultaneous secretion and reabsorption by active transport Acta Physiol Scand 52 276 1961
2 Berglund F Kallander J & Pompeius R Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man J Urol 114 802 1975
3 Blackwood W S Maudgal D P Pickard R G Lawrence D & Northfield T C Cimetidine in duodenal ulcer Lancet 2 174 1976
4 Bodemar G & Walan A Maintenance treatment of recurrent peptic ulcer by cimetidine Lancet 1 403 1978
5 Brochner Mortensen J A simple method for the determination of glomerular filtration rate Scand J Clin Lab Invest 30 271 1972
6 Brochner Mortensen J Giese J & Rossing N Renal inulin clearance versus total plasma clearance of [51Cr]EDTA *Scand J Clin Lab Invest 23 301 1969*
7 Brochner Mortensen J & Rodbro P Optimum time of blood sampling for determination of glomerular filtration rate by single injection [51Cr]EDTA plasma clearance Scand J Clin Lab Invest 36 795 1976
8 Bucht H On the tubular excretion of thiosulphate and creatinine under the influence of caronamide Scand J Clin Lab Invest 1 270 1949
9 Burland W L Duncan W A M Hesselbo T Mills J G Sharpe P C Haggie S J & Wyllie J H Pharmacological evaluation of cimetidine a new histamine H2-receptor antagonist in healthy man Br J Clin Pharmacol 2 481 1975
10 Burland W L Gleadle R I Mills J G Sharpe P C & Wells A L The effect of cimetidine on renal function In Cimetidine (ed W L Burland and M A Simkins) p 67 Excerpta Medica Amsterdam and Oxford 1977
11 Burry H C & Dieppe P A Apparent reduction of endogenous creatinine clearance by salicylate treatment Br Med J 2 16 1976
12 Doherty C C O Connor F A Buchanan K D & McGeown M G Cimetidine for duodenal ulceration in patients undergoing hemodialysis Br Med J 2 1506 1977
13 Doolan P D Alpen E L & Theil G B A clinical appraisal of the plasma concentration and endogenous clearance of creatinine Am J Med 32 65 1962
14 Dubb J W Stote R M Familiar R G Lee K & Alexander F Effect of cimetidine on renal function in normal man Clin Pharmacol Ther 24 1 76 1978
15 Dutt M Sandersson P & Northfield T C Effect of cimetidine on renal function in man Gut 19 5 A441 1978
16 Haggie S J Fermont D C & Wyllie J H Treatment of duodenal ulcer with cimetidine Lancet 1 983 1976
17 Jones R H Levin M R & Parsons V Therapeutic effect of cimetidine in patients undergoing haemodialysis Br Med J 1 650 1979
18 Jones R H Rudge C J Bewick M Parsons V & Weston M J Cimetidine prophylaxis against upper gastrointestinal haemorrhage after renal transplantation Br Med J 1 398 1978
19 Kirchman K H Cutler R E & Blair A D Pharmacokinetics of cimetidine in normal and uremic humans Clin Res 27 (1) 73A 1979
20 Larsson R Bodemar G & Kågedal B The effect of cimetidine a new histamine H2-receptor antagonist on renal function Acta Med Scand 205 87 1979
21 Larsson R Bodemar G & Norlander B Oral absorption of cimetidine and its clearance in patients with renal failure Eur J Clin Pharmacol 15 153 1979
22 Mudge G H Berndt W O & Valtin H Tubular transport of urea glucose phosphate uric acid sulfate and thiosulfate In Handbook of Physiology section 8 (ed S R Geiger) Renal physiology chapter 19 587 American Physiological Society 1973
23 Norlander B Bodemar G & Walan A Therapeutic blood concentrations and renal excretion of cimetidine Scand J Gastroenterol *In press 1980*
24 Shannon J A The renal excretion of creatinine in man J Clin Invest 14 463 1935
25 Shannon J A & Ranges H A On the renal tubular excretion of creatinine in normal man J Clin Invest 20 169 1941
26 Yu T F & Gutman A B Paradoxical retention of uric acid by uricosuric drugs in low dosage Proc Soc Exp Biol Med 90 542 1955

Serum and Urinary Myoglobin in Alcoholics

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ABSTRACT The serum levels of myoglobin were measured in 106 male alcoholics Subnormal levels were found in 31% of the alcoholics with no alcohol onsumption for the last 2–4 weeks while none of hem had elevated levels Of the alcoholics on am oulatory control and with varying current alcohol ntake, 18% had increased levels compared to iealthy controls Serial myoglobin levels were deter mined in 19 patients following the cessation of heavy lrinking sprees Despite the fact that none of the pa ients had clinical evidence of acute myopathy, narked myoglobin elevations were noted in five pa ients their serum levels gradually declined and normalized within 4–7 days Comparing the three roups similar frequencies of subnormal or elevated erum CK levels were observed Myoglobin levels vere not raised due to impaired glomerular filtration ates No correlation was found between serum myo lobin and laboratory signs of liver affection Al hough hypophosphatemia, hypomagnesemia and iypokalemia were occasionally noted decreased erum electrolytes did not have any relation to ele ated serum myoglobin A transient slightly ncreased urinary excretion of myoglobin parallel vith increased excretion of β_2-microglobulin was observed in 2/17 alcoholics, suggesting that instances of nyoglobinuria in alcoholics with heavy recent drink ng may be due to *a transient minor tubular dys-* unction

ey words alcoholics serum myoglobin urinary myo- lobin liver kidney

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The circulating levels of the low molecular weight ieme protein myoglobin have been reported to be levated in conditions with damage to striated or nyocardial muscles (5 9 23) The elimination of nyoglobin from the circulation occurs mainly by he renal route (1 6) but evidently to some extent ilso by the liver (1 21) Hence elevated serum nyoglobin is observed in patients with renal failure (6) and slightly elevated in patients with hepatic failure (21) In alcoholics both acute and/or chronic myopathies are observed (8) and accompanied by elevated creatine kinase (CK) levels (14) We report here the frequency of pathological myoglobinemia in alcoholics and the changes in serum myoglobin after a period of excessive drinking possibly in volving a disturbed elimination rate for this protein

It has been argued that disturbance of the elec trolyte balance is a mechanism underlying the myopathies of alcoholics (12 15 20) An attempt was therefore made to correlate elevated myoglobin levels to serum concentrations of various electrolytes Since myoglobinuria has previously been re ported in single cases with heavy alcohol consump tion (7 25) we also investigated the urinary excre tion of myoglobin after alcohol abuse The urinary excretion of β_2 microglobulin another low mol wt protein normally almost completely reabsorbed by the proximal tubules (19) was simultaneously measured in order to elucidate whether myo globinuria in alcoholics might be due to tubular dys function

PATIENTS AND METHODS

This study comprised three groups of male alcoholics *Group A* consisted of 42 non selected chronic alcoholics (mean age 43 range 24–67 years) who due to excessive drinking were admitted involuntarily for institutional care at Venngarn County of Stockholm Sweden They had histories of alcoholism of 7–20 years duration Serum samples were collected from these patients 2–4 weeks after admission during which time they had been pre vented from taking alcohol *Group B* consisted of 19 in patients with histories of alcoholism of 5–20 years ad mitted to the Department of Psychiatry Uppsala after a

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Abbreviations CK = creatine kinase ALAT = alanine aminotransferase ASAT = aspartate aminotransferase γ GT = gamma glutamyl transferase GFR = glomerular filtration rate

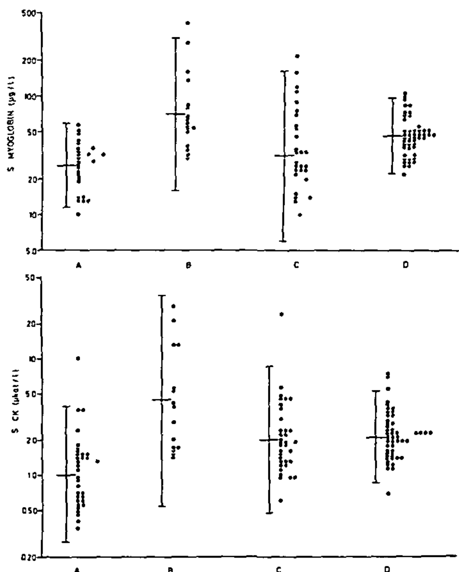


Fig 1 Mean levels of myoglobin and CK in sera of male alcoholics (*A B C*) and healthy age matched men (*D*) Geometric means of myoglobin (ranges expressed as 95% confidence limits) were for group A 26 0 (11 5–58 7) group B 71 2 (16 2–312 3) group C 32 5 (6 4–165 3) group D 47 3 (22 6–98 8) µg/l Corresponding means (ranges) for CK were for group A (0 27–3 93) group B 4 4 (0 55–35 36) group C 2 (0 47–2 49) group D 2 1 (0 82–5 43) µkat/l

period of alcohol abuse of 3–16 weeks Individuals in this group had on average consumed 340 g alcohol/day (range 180–480) during the week prior to admission and were monitored by serial determinations during 14–16 days from admission to hospital They were treated with chlormethiazole during the first week and disulfiram daily during the observation period Two patients developed delirium tremens at the beginning of the study Sera were collected at least three times and from the majority of patients on eight occasions during the observation period Urine was collected during 24 hours on days 1 7 and 14
Group C Serum samples were collected on one occasion from 45 consecutive out patients (mean age 41 range 21–62 years) with alcoholism of varying duration (5–20 years) ambulatory-controlled as part of a voluntary weaning program at the Department of Psychiatry University Hospital Uppsala Sweden The degree of alcohol con sumption during the period nearest blood collection probably varied within wide limits and approximately 20% of the patients were treated with disulfiram

*All sera were subjected to the following analyses (r*ence ranges are given in parentheses with 95% confid limits) Alanine aminotransferase (ALAT) (<0 6 µk and aspartate aminotransferase (ASAT) (<0 6 µkat/l cording to the methods recommended by the Comm on Enzymes of the Scandinavian Society for Cli Chemistry and Clinical Physiology (22) The coeffici of variation of the methods were 1 5 and 2% respect ly Bilirubin (0 8–4 8 µkat/l) according to Michaelsson with a coefficient of variation of 2% CK and γ gluta transferase (γ GT) (<1 0 µkat/l for males) were meas with commercially available kits and according to manufacturer s instructions (Boehringer Mannheim Germany) The coefficients of variation for the meth were 4 and 3% respectively Creatinine (64–106 µmo was measured by an autoanalyser technique (Technicon 11 b) The coefficient of variation for the method approximately 2% Myoglobin was measured as previo ly described (21) by a radioimmunosorbent assay T coefficient of variation for the assay was 7%

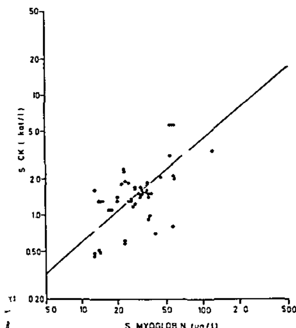


Fig. 2. Serum levels of myoglobin and CK in the 106 alcoholics illustrated in Fig. 1. The equation for the regression line is log CK=0.861 log myoglobin −1.086, coefficient of correlation 0.79 ($p<0.001$).

The sera obtained from the longitudinally studied 19 in patients were also analysed for the following electrolytes: calcium (1.44–2.20 mmol/l), potassium (3.2–5.1 mmol/l), magnesium (0.65–1.00 mmol/l) and phosphate (0.76–1.44 mmol/l). Calcium and magnesium were analysed by an atomic absorption spectrophotometric method, potassium by flame photometry and phosphate by an autoanalyser technique (Technicon). The coefficients of variation of the methods were 1.5, 2, <1.0 and 2% respectively.

An i.v. galactose tolerance test was performed on the 19 in patients on the 8th or 10th day after admission. The test, which was performed according to Tengström (24), using 1.94 mmol/galactose/kg body mass, has in our laboratory an upper $T_{\frac{1}{2}}$ limit of 17 min for a normal adult.

Urine specimens were collected in plastic bags of 2 l capacity with two ml of a preservative solution (2 mol/l Tris HCL buffer, pH 8 with 0.2% sodium azide) and analysed for β_2-microglobulin and myoglobin (21). The normal excretion of β_2-microglobulin is 30–370 μg/24 hours and for myoglobin <5 μg/24 hours.

Student's *t* test was used for statistical analyses on groups or paired values.

RESULTS

Serum and urinary myoglobin concentrations

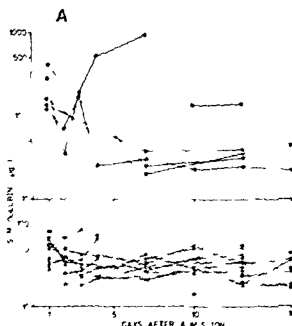
Fig. 1 shows serum myoglobin concentrations in 57 healthy male controls and 106 male alcoholics, the latter divided into three groups. 18% of the ambulatory-controlled patients (group C) had myoglobin values above the reference range. None of the in patients who had not consumed alcohol for 2–4 weeks (group A) had elevated serum myoglobin levels. As a group they had significantly reduced serum myoglobin concentrations compared with the controls ($p<0.001$) and 31% of the patients had subnormal values. Group B, which comprised 19 alcoholics admitted to the hospital due to excessive drinking in recent weeks, was followed by serial serum determinations from the day after admission. At the time of the first serum sample five of the patients had elevated myoglobin levels, while the others had levels within the control range. Serial determinations showed a uniform pattern of declining myoglobin values during the first week after admission, with a few exceptions. An initial decline was followed by a sharp rise in serum myoglobin in two patients. All elevated serum levels normalized within the observation period of 2 weeks.

A significant correlation ($r=0.79$, $p<0.001$) was found between serum CK and serum myoglobin concentrations (Fig. 2) and the frequency of serum CK outside the control range was quite similar among the alcoholics (for the whole material as well as for the three groups) to that of myoglobin (Fig. 1). Serial determinations of serum CK also revealed the same pattern of changes as for serum myoglobin (Fig. 3). Two patients developed delirium tremens on the second day after admission but no rise in serum myoglobin or CK was observed in connection with these attacks.

Only two patients had urinary excretion of myoglobin above the upper normal limit on the first day. These two patients also had increased urinary excretion of β_2-microglobulin (>370 μg). The urinary excretion of both proteins returned to normal during the observation period (Fig. 4). None of the patients had clinical signs of muscle affection such as severe muscle tenderness, edema or apparent weakness.

Relation of kidney and liver function to serum myoglobin

No patient in the entire material had an impaired glomerular filtration rate (GFR) as judged from serum creatinine, nor were any significant changes observed in this variable in the patients who were followed by serial determinations, indicating that



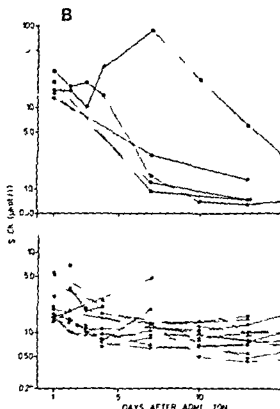


Fig 1 (A) Serial determinations of myoglobin in 19 alcoholics admitted to hospital after a period of excessive drinking divided into two subgroups on the basis of serum myoglobin on admission one with elevated serum m globin (>98 8 µg/l) and the other with serum myoglo within the control range (B) Serial determinations of (

elevated serum myoglobin could not be attributed to an impaired GFR

Another cause of disturbed myoglobin elimination could be reduced liver function The mean serum concentrations of liver enzymes and bilirubin in the three groups of alcoholics are listed in Table I Although signs of liver affection were frequent findings there was no correlation between the serum levels of myoglobin and bilirubin (r=0 06) ASAT (r=0 14) or γ GT (r=0 22) Six of the longitudinally followed in patients had impaired galactose elimination rates but no correlation was found between this estimate of liver function and serum myoglobin concentrations on days 1 or 10 (r=0 34 and 0 24 respectively)

Relation of serum electrolytes to serum myoglobin

On admission we observed in a few of the serially followed patients slightly reduced (within the minus 2 to 3 S D intervals) serum concentrations of phosphate (4 cases) potassium (3 cases) and magnesium (3 cases) By the fourth day the concentrations had normalized Significant increments (p<0 05) in re tion to the first value were found for phosphate days 4 and 7 and for potassium on day 13 (Table However no correlation was found betw myoglobin and electrolyte levels Nor did analy of the individual values give rise to the suspicion any connection between changes in serum myog bin and electrolytes

DISCUSSION

The analysis of serum concentrations of myoglo in male alcoholics shows that the circulating lev of this protein are elevated in a considera number of patients without clinical myopath Muscle affections in alcoholism are rare entities the clinically recognizable forms of acute a chronic alcoholic myopathy (8) However subcl cal myopathy as detected by estimation of CK reported in 38–84% of chronic alcoholics (13 1 17 26) In this study a comparison of serum leve of myoglobin and CK showed excellent agreeme

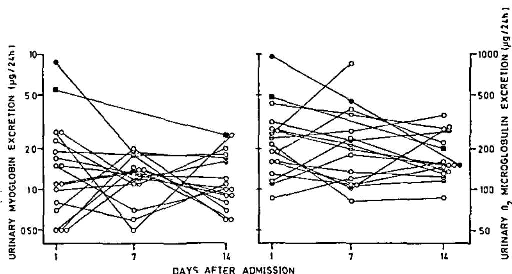


Fig 4 Urinary excretion of myoglobin and β microglobulin during a 2 week abstinence period in 17 alcoholics admitted to hospital after heavy drinking ● ■ = Patients with increased urinary excretion of myoglobin (>5 µg/24 hours) The upper limit of normal excretion for β microglobulin is 370 µg/24 hours

suggesting that previous reports on CK values in alcoholics are comparable with present data on myoglobin Taken as a whole 10% of the alcoholics in this study had elevated myoglobin levels However when the patients were divided into three groups according to the probability and degree of current alcohol consumption or abstention from alcohol quite different frequencies were obtained In the group of chronic alcoholics who had received institutional care and been without alcohol intake for 2–4 weeks nobody had elevated serum myoglobin or CK while about one third had subnormal serum concentrations In the group of chronic alcoholics with heavy alcohol consumption until admission 26% had pathologically raised serum myoglobin concentrations Of the alcoholics under ambulatory control in an alcohol weaning program and with vague or uncertain information as to the true alcohol intake 18% had elevated serum myoglobin values Serial determinations of myoglobin and CK in alcoholics after alcohol abuse showed their steady parallel decrease and final normalization 4–7 days after admission and withdrawal of alcohol

Myoglobin is mainly eliminated by the renal route (6) but animal experimental studies (1) and our previous observations (21) indicate that myoglobin also to a minor extent is eliminated by the liver The possibility that impaired renal function influenced our results can be ruled out Although many of the patients had laboratory signs of impaired liver function we found no correlation between the myoglobin levels and the degree of liver affection Taken together this suggests that elevated myoglobin is caused mainly by increased myoglobin release from muscles indicating a muscular affection which in view of the rapid normalization of serum myoglobin appears to be quite temporary after withdrawal of

Table I *Laboratory liver findings*

The values are given as arithmetic means ± S D

	Bilirubin (µmol/l)	ASAT (µkat/l)	ALAT (µkat/l)	γ GT (µkat/l)	$T\frac{1}{2}$ galactose (min)
Group A	9 09±7 25	1 12+0 94	1 25±1 14	2 94±2 75	–
Group B	7 19±5 30	0 79±0 67	0 83±0 66	2 33±2 80	
Group C	12 55±4 27	1 56±1 13	1 21±0 80	2 50±2 26	

Table II. *Serum electrolytes in alcoholics serially followed from start of abstinence (mean ± S.D.)*

	Day			
	1	4	7	13
Phosphate	0.95±0.21	1.10±0.31	1.16±0.24	1.08±0.25
Calcium	2.42±0.17	2.30±0.17	2.44±0.16	2.46±0.11
Potassium	3.74±0.64	3.95±0.41	4.03±0.48	4.28±0.47*
Magnesium	0.75±0.15	0.77±0.09	0.84±0.10	0.80±0.10

* Significant increment ($p<0.05$) compared with day 1 and calculated on paired values.

alcohol. In contrast, the subnormal myoglobin levels found in alcoholics may persist at least a month with total abstinence, possibly reflecting a reduced muscle mass due to malnutrition or, alternatively, a more chronic atrophic muscular disorder induced by alcohol. The reports on clinically overt myopathies also indicate that patients with acute alcoholic myopathy recover rapidly and evidently completely but that patients with long-lasting alcoholic myopathy have muscular disability for longer periods after discontinued drinking (8).

The pathogenesis of the muscular affection in alcoholics is not yet clear. Among the hypotheses suggested one could mention prolonged ischemia (3), nutritional deficiency (2), depression of glycolytic enzymes (18) and destruction of the muscle cell membranes and mitochondria (11). It has also been suggested that there is a primary disturbance of water and electrolyte metabolism in chronic alcoholics with secondary development of intracellular edema and cell damage. Since hypokalemia, hypomagnesemia and hypophosphatemia are known to occur in alcoholism (12, 15, 20) and all are known to be associated with changes in muscle function and/or histology (4, 20), we searched for a relationship between the serum levels of these electrolytes and myoglobin. We observed hypophosphatemia as well as hypomagnesemia and hypokalemia in certain alcoholics on admission and also significant increments with time in the concentrations of phosphate and potassium in the entire patient group. However, we found no correlation between myoglobin levels and serum electrolytes. Deficiency of these electrolytes may contribute to the muscular affection but it does not seem to be the primary cause of elevated serum myoglobin or CK in alcoholics.

Individual cases with the most dramatic form of acute alcoholic myopathy, alcoholic rhabdomyolysis, are reported to have myoglobinuria and also acute renal failure (7, 25). The develo[illegible] ment of a radioimmunoassay for the measureme[illegible] of low concentrations of myoglobin in urine (21) h[illegible] enabled the study of urinary myoglobin excretion [illegible] alcoholics before the appearance of acute seve[illegible] myopathy. We found that 2/17 cases had myoglob[illegible] excretion above the control range after rece[illegible] drinking. However, in these cases we also found [illegible] increased excretion of β_2-microglobulin—a mark[illegible] of tubular function (19)—which normalized aft[illegible] four days of alcohol abstinence, as did the myogl[illegible] bin excretion. These data are in accordance wi[illegible] previous observations indicating a fairly high ren[illegible] threshold for myoglobin in normal situations b[illegible] an increased excretion in situations with tubul[illegible] dysfunction (10). Thus, the present results sugge[illegible] that a transient tubular affection may be seen [illegible] alcoholics and, as a secondary phenomenon, i[illegible] creased urinary output of myoglobin.

Whether the detection of elevated serum myogl[illegible] bin or CK as a single sign of muscular affection [illegible] alcoholics is of clinical value is at present unsettle[illegible] Moreover, there are some arguments against th[illegible] estimation of serum myoglobin as a screening te[illegible] for alcoholic myopathy. Muscular exercise ma[illegible] provoke a slight increase in serum myoglobin (21[illegible] and alcoholics usually have tremors and seizure[illegible] during the withdrawal period. These conditions ap[illegible] pear to be minor contaminants, judging from the lack of a rise of myoglobin in two patients durin[illegible] attacks of delirium tremens. However, many al[illegible] coholics are admitted to hospital due to trauma an[illegible] since traumatic muscular damage certainly pro[illegible] duces highly elevated myoglobin levels, this is [illegible] factor to consider. In selected patients with clinica[illegible] suspicion of severe acute or chronic alcoholic myopathy, estimation of serum and urinary myo[illegible] globin may be of importance. At present it ca[illegible] clearly be stated that heavy drinkers with acute dif[illegible] fuse chest pains present a differential diagnosis

problem when serum myoglobin determination is used as an acute diagnostic test of myocardial in farction

ACKNOWLEDGEMENTS

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REFERENCES

1 Amako T Koga J Kobayashi A Urakado S & Tokunaga J Experimental investigation of the metabolism of myoglobin Kyushu J Med Sci 14 277 1963

2 Dimberg R Hed R & Nygren A Liver muscle enzyme activities in the serum of alcoholics on a diet poor in carbohydrates Acta Med Scand 181 227 1967

3 Douglas R M Fewings J D Casley Smith J R & West R R Recurrent rhabdomyolysis precipi tated by alcohol A case report with physiological and electronmicroscopic studies of skeletal muscles Aust Ann Med 15 251 1966

4 Fuller T J Carter N W Barcenas C & Knochel J P Reversible changes of the muscle cell in experi mental phosphorus deficiency J Clin Invest 57 1019 1976

5 Hallgren R Cullhed I Roxin L E & Venge P Myoglobinemia after myocardial infarction—influ ence of renal function Eur J Cardiol 8 607 1978

6 Hällgren R Karlsson F A Roxin L E & Venge P Myoglobin turnover—influence of renal and ex tra renal factors J Lab Clin Med 91 246 1978

7 Hed R Three cases of non familial myoglobinuria Acta Med Scand (Suppl) 303 86 1955

8 Joong S Alcoholic myopathy A critical review Ala J Med Sci 9 79 1972

9 Kagen L J Myoglobin Biochemical physiological and clinical aspects Columbia University Press London 1973

10 Karlsson F A Roxin L E Venge P & Wibell L *Evaluation of* urinary myoglobin assay test for myocardial infarction Scand J Clin Lab Invest 38 717 1978

11 Klinkerfuss G Bleisch V Dioso M M & Perkoff G T A spectrum of myopathy associated with al coholism II Light and electronmicroscopic observa tions Ann Intern Med 67 493 1967

12 Knochel J P Bilbrey G L Fuller T J & Carter N W The muscle cell in chronic alcoholism The possible role of phosphate depletion in alcoholic myopathy Ann NY Acad Sci 252 274 1975

13 Konttinen A Hartel G & Louhija A Multiple serum enzyme analyses in chronic alcoholics Acta Med Scand 188 257 1970

14 Lafair J S & Myerson R M Alcoholic myopathy with special reference to the significance of creatine phosphokinase Arch Intern Med 122 417 1968

15 Martin J B Craig J W Eckel R E & Munger J Hypokalemic myopathy in chronic alcoholism Neurology *21 1160 1971*

16 Michaelsson M Evaluation of a method for deter mination of bilirubin in serum using direct spec trophotometry Scand J Clin Lab Invest 30 387 1972

17 Nygren A Serum creatine phosphokinase activity in chronic alcoholism in connection with acute alcohol intoxication Acta Med Scand 179 623 1966

18 Perkoff G T Hardy P & Velez Garcia E Re versible acute muscular syndrome in chronic al coholism N Engl J Med 274 1277 1966

19 Peterson P A Evrin P E & Berggård I Differen tiation of glomerular tubular and normal proteinuria by determinations of urinary excretion of β micro- globulin albumin and total protein J Clin Invest 48 1189 1969

20 Roelofs R J & Engel W K Myopathies associated with systemic disease Postgrad Med 50 95 1971

21 Roxin L E Venge P Friman G & Hallgren R Radioimmunoassays of human myoglobin in serum and urine Scand J Clin Lab Invest 39 37 1979

22 Scandinavian Society for Clinical Chemistry and Cli nical Physiology Recommended methods for the de termination of four enzymes in blood Scand J Clin Lab Invest 33 291 1974

23 Stone M J Waterman M R Harimato D Mur ray G Wilson N Platt M R Blomquist G & Willerson J T Serum myoglobin level as diagnostic test in patients with acute myocardial infarction Br Heart J 39 375 1977

24 Tengstrom B An intravenous galactose tolerance test and its use in hepatobiliary disease Acta Med Scand 183 31 1968

25 *Valatis J Pilz C G Olner H & Chomet B* Myoglobinuria myoglobinuric nephrosis and al coholism Arch Pathol 70 195 1960

26 Velez Garcia E Hardy P Dioso M & Perkoff G Cysteine stimulated serum creatine phospho- kinase unexpected results J Lab Clin Med 68 638 1966

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Serum Lipids with Special Reference to HDL Cholesterol and Triglycerides in Young Male Survivors of Acute Myocardial Infarction

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ABSTRACT Serum cholesterol triglycerides and high density l poprotein (HDL) cholesterol were de ermined in 56 male survivors of myocardial infarc ion (MI) suffered 6–20 months earl er and in 82 healthy age and sex matched controls The mean age of both groups was 39 years Total serum cholesterol was within normal limits in both groups whereas HDL cholesterol was considerably lower and tri lycerides remarkably elevated in MI patients com pared with the controls Judging from previous and resent data low HDL cholesterol seems to be a oronary risk factor as such This study indicates that ow HDL cholesterol and especially a low HDL holesterol/total cholesterol ratio may be stronger oronary risk factors than total serum cholesterol alone Because HDL cholesterol and triglycerides were inversely correlated these results also em phasize the importance of serum triglycerides as a risk factor for coronary heart disease

Key wo ds Cholesterol triglycerides h gh-dens ty l poprote n myocardial nfarct on

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During the last five years plasma high density lipo protein (HDL) cholesterol has received increas ng attention as an independent risk factor for coronary heart d sease (CHD) (10 12 15) In the early 50s ow α l poprote n levels (i e HDL) were found in assoc at on with CHD even in young males (13 14) Unfortunately triglycerides were not common y measured at that time Later work on the role of ip ds in CHD ma nly focused on plasma total holesterol Elevated triglycerides have only occa ionally been associated with an increased occur ence of CHD

Since triglycerides and HDL cholesterol have been found to be inversely related (17) the present work was undertaken to elucidate the role of total cholesterol HDL cholesterol and triglycerides in young male survivors of acute myocardial infarc tion (MI)

PATIENTS AND METHODS

F fty s x male subjects (mean age 39 years range 24–45) were stud ed 6–20 months after def n te MI They had been treated n the Departments of Med c ne Un vers ty Central Hosp tal of Hels nki and d agnoses were estab l shed from cl n cal h stories serial ECGs and blood analyses fulf ll ng the WHO criteria (19) Th s was the f rst infarct on in these patients and none had d abetes mell tus During hosp tal zat on rout ne d etary instruc t ons were given to all subjects At the t me of the p esent nvest gation 34 pat ents reported that they had s gn f cantly reduced the use of saturated fats and/or carbohy drates after MI β-Block ng drugs were used by 39 pa t ents (p ndolol 22 propranolol 7 metoprolol 7 alprenolol 3) D uret cs were g ven to 8 pat ents

The control group cons sted of 82 healthy male subjects w th various occupat ons s m lar to those of the MI pa tients The r mean age was 39 years (range 29–50)

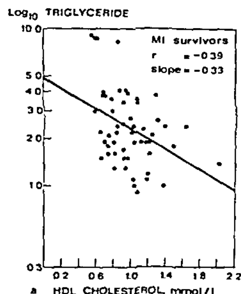
Venous blood was drawn for blood analyses after an overn ght fast Serum total cholesterol (1) triglycerides (9) and HDL cholesterol us ng prec p tat on by the PEG-6000 method (18) were determ ned The d v s on of hyperl poprote nem as nto subgroups was made accord ing to the WHO recommendat on (2) Serum total choles terol and triglycerides were regarded as elevated at or above 7 0 and 1 7 mmol/l respect vely

RESULTS

Serum total cholesterol and triglycerides HDL cholesterol and the percentage HDL cholesterol of total cholesterol are given in Table I Mean serum

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Abbre at ons HDL h gh-dens ty l poprote n CHD coronary heart d sease MI myocard al nfarct on LPL l poprote n l pase



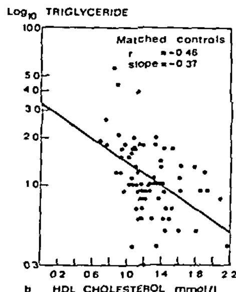


Fig 1 Relationship between $\log_{10}$ serum triglycerides and HDL cholesterol for MI survivors (*a*) and controls (*b*)

total cholesterol was within normal limits in MI patients though significantly higher than in controls However mean serum triglycerides were remarkably high and HDL cholesterol was very low in MI survivors compared to the controls The HDL cholesterol levels of both MI survivors and matched controls were inversely correlated with the log of triglycerides ($r=-0$ 39 and -0 46 respectively) (Fig 1) The slope of the regression line was steeper in controls than in MI patients

Thirty nine patients (70%) were treated with β blocking drugs Their mean HDL cholesterol (± S D) was 0 98±0 21 mmol/l which did not differ from the mean value of the non users (0 92±0 25 mmol/l)

DISCUSSION

Serum lipid and lipoprotein levels change during acute MI but return to their normal values within 2–3 months (7 16) The time of entering the stu therefore important In the present study lipids and lipoproteins were measured 6–20 after infarction which is long enough not to date the results

The present investigation indicated type hyperlipoproteinemia in only 7% of the MI vivors This is a remarkably low incidence pared with the figure of 22% for an unsel Finnish population of the same age and sex (3)

The MI survivors comprised all male MI pat in this age group who were admitted to this hos during the stated period excluding those who in the acute phase It is improbable that a the latter would have had type II A hyper proteinemia Gustafson et al (11) reported type hyperlipoproteinemia in 17% of MI survivors w determined one year after MI

Serum total cholesterol is considered to b

Table I *Serum lipids and HDL cholesterol (mmol/l mean ± S D) in MI survivors and controls*

	n	HDL cholesterol	Total cholesterol	% HDL cholesterol	Triglycerides
MI survivors	56	0 98±0 28 *	6 6±1 2 *	15 2	2 6±1 8
Normal lipids	13	1 11±0 33	5 9±0 6	18 8	1 3±0.2
II A	4	0 89±0 15	7 6±0 5	11 8	1 3±0 3
II B	20	0 93±0 25	7 9±0 9	11 9	3 2±1 9
IV	19	0 97±0 27	5 8±0 6	16 9	3 3±1 9
Controls	82	1 31±0 30	5 4±0 9	24 2	1 0±0 4

* $p<0$ 001 for the difference between MI survivors and controls

rong coronary risk factor especially in young ien Opinions on triglycerides have varied Hyper iglyceridemia with or without associated hyper iolesterolemia occurred in 70% of our MI sur ivors which is in agreement with earlier studies iat have stressed serum triglycerides as a coronary sk factor (4 5 20)

Recently epidemiological evidence from studies Hawaii Framingham Norway etc have in icated an inverse relationship between HDL iolesterol and CHD (10 12 15) Our findings dicating markedly low HDL cholesterol values in oung male survivors of MI compared with con ols are in agreement with previous data derived om different populations HDL cholesterol levels both MI patients and controls were inversely lated to triglyceride levels as noted previously 7) HDL cholesterol arises as a result of lipopro in lipase (LPL) activity from very low density poprotein The correlation between the activity of LPL and HDL cholesterol is positive but it is eggested that the ability of HDL to activate LPL is in hypertriglyceridemic states (6) On the ther hand it has been found that a reduction of rum triglycerides does not increase HDL choles rol (8)

Il Our findings indicate that HDL cholesterol and e HDL cholesterol/total cholesterol ratio are onger coronary risk factors than total cholesterol one in young men with previous MI More con rmation is however needed as to whether the duction of HDL cholesterol really precedes the set of clinical CHD

REFERENCES

Badzio T & Boczon H The determination of free and esterified cholesterol in blood after separation by thin layer chromatography Clin Chim Acta 13 794 1966

Beaumont J L Carlson L A Cooper G R Fejfar Z Fredrickson D S & Strasser T Clas sification of hyperlipidemias and hyperlipoprotein emias Bull WHO 43 89 1970

Björkstén F Aromaa A Eriksson A W Maatela J Kirjarinta M Fellman J & Tamminen M Serum cholesterol and triglyceride concentrations of Finns and Finnish Lapps Acta Med Scand 198 23 1975

Carlson L A Serum lipids in men with myocardial infarction Acta Med Scand 167 399 1960

5 Carlson L A & Bottiger L E Ischaemic heart disease in relation to fasting value of plasma tri glycerides and cholesterol Lancet 1 865 1972

6 Chan M K Varghese Z Persaud J W & Moorhead J F Do plasma triglycerides regulate high-density lipoproteins or vice versa? Lancet 2 305 1979

7 Dodds C & Mills G L Influence of myocardial infarction on plasma lipoprotein concentration Lan cet 1 1160 1959

8 Elkeles R S Effect of treatment of hypertri glyceridaemia on high and low density lipoprotein cholesterol concentrations Lancet I 980 1979

9 Fletcher M J A colorimetric method for estimated serum triglycerides Clin Chim Acta 22 393 1968

10 Gordon T Castelli W P Hjortland M C Kan nel W B & Dawber T R High density lipoprotein as a protective factor against coronary heart disease The Framingham Study Am J Med 62 707 1977

11 Gustafson A Elmfeldt D Wilhelmsen L & Tibblin G Serum lipids and lipoproteins in men after myocardial infarction compared with representative population sample Circulation 46 709 1972

12 Miller N E Førde O H Thelle D S & Mjøs O D The Tromsø heart study High-density lipopro- tein and coronary heart-disease a prospective case control study Lancet 1 965 1977

13 Nikkila E Studies on the lipid–protein relationship in normal and pathologic sera and the effect of heparin on serum lipoproteins Scand J Clin Lab Invest (Suppl) 5 8 1953

14 Oliver M F & Boyd G S Serum lipoprotein pat terns in coronary sclerosis and associated conditions Br Heart J 17 299 1955

15 Rhoads G G Gulbrandsen C L & Kagan A Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men N Engl J Med 294 293 1976

16 Rönnemaa T Viikari J Irjala K & Peltola O Changes in serum high density lipoprotein cholesterol concentration during acute myocardial infarction Third Scandinavian Symposium on Atherosclerosis Research Turku 1979

17 Schaefer E J Levy R I Anderson D W Dan ner R N Brewer H B Jr & Blackwelder W C Plasma triglycerides in regulation of H D L -choles terol levels Lancet 2 39 1978

18 Viikari J Precipitation of plasma lipoproteins by PEG 6000 and its evaluation with electrophoresis and ultracentrifugation Scand J Clin Lab Invest 36 265 1976

19 Working Group of Ischaemic Heart Disease Registers 1971 Copenhagen Report of the 5th working group with second revision of the operating protocol Regional Office for Europe WHO Euro 5010(5) Copenhagen 1971

20 Zilversmit D B Atherogenesis a postprandial phenomenon Circulation 60 473 1979

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Effect of Guar Gum on Body Weight and Serum Lipids in Hypercholesterolemic Females

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BSTRACT The effect of guar gum (15 g/day) on rum lipids and body weight of middle aged hyper olesterolemic females was studied in a double blind ntrolled trial No consistent changes were observed serum cholesterol, triglycerides or HDL cholesol in patients taking guar gum placebo or no dication at all A highly significant decrease in dy weight (62 9±2 1 vs 60 4±2 2 kg, $p<0$ 0005, ired comparison) was seen in subjects receiving ar gum, whereas body weight remained constant in other two groups It is concluded that the daily estion of 15 g of guar gum results in a permanent ight loss but does not influence serum lipids in nales with hypercholesterolemia

words guar gum dietary fiber weight loss serum ds

ta Med Scand 208 45 1980

nas been suggested that low intake of dietary fiber one of the factors responsible for the high preva ice of coronary heart disease in western society 11) The fiber hypothesis is partially supported epidemiological studies indicating an association *tween* the intake of fiber containing foodstuffs d the incidence of ischemic heart disease (8) irthermore there is some evidence that diet rich fiber may protect against the risk factors of ierosclerosis like dyslipidemia obesity and dia tes (11 12 13)

Despite numerous investigations it is not yet clear iether fiber added to the modern diet influences dy weight or serum lipoprotein levels (7) The nflicting results are probably due to several fac s Firstly it is becoming increasingly clear that effects of various kinds of fibers are not identi l Secondly the experimental design used in se investigations has not always been satisfac y in the absence of an adequate control group confounding factors like seasonal variation are likely to distort the results

We report on the effects of guar gum a viscous fiber containing galactose and mannose on serum lipoproteins and body weight The results of the randomized double blind study suggest that inges tion of moderate amounts of guar gum before meals *induces weight loss but does not affect serum lipids* in middle aged hypercholesterolemic females

STUDY POPULATION AND METHODS

Subjects and design of the study

The subjects were recruited from a group of individuals with hypercholesterolemia detected in a screening opera tion aimed at primary prevention of coronary heart dis ease Before entering the trial all subjects received diet instructions recommending a reduction of the use of satu rated fats and simple carbohydrates and avoidance of ex cessive alcohol consumption Weight loss was not encour aged Antihypercholesterolemic medication if there was any was discontinued at least one month before the baseline measurements Informed consent was obtained from all participants before the beginning of the investiga tion

All subjects visited the municipal health center for blood lipid measurements three times at 4-week intervals before the trial A total of 33 females with serum choles terol levels above 7 6 mmol/l in all determinations were included in the study and were randomized into three *experimental groups guar gum (group A) placebo (group* B) and no treatment (group C) One subject in group A did not complete the trial for an unspecified reason Her val ues are not included in the calculations

A double blind experimental design was used in the comparison of groups A and B The subjects took either 5 g of guar gum or a placebo preparation (wheat flower containing no fiber) similar in appearance three times a day before meals Guar gum was administered in granules 1 g containing 0 73 g of pure guar gum (Remeda Phar maceutical Co Kuopio Finland) The patients were advised to mix the preparations w

Table I *Serum cholesterol concentration (mmol/l) in groups A B and C during the trial (mean±S E M*

Group	Before treatment	Months after the beginning of treatment			
		1	2	3	4
A (n=10)	8 28±0 39	7 89±1 16	8 51±1 24	7 67±0 91	8 00±0 73
B (n=11)	9 40±0 26	8 63±0 38	8 43±0 56	8 83±0 62	9 04±0 41
C (n=11)	9 13±0 49	-	-	-	8 67±0 47

food or drink The subjects in group C did not take any medication during the trial

Techniques

Total serum cholesterol body weight and blood pressure were measured three times at one month intervals before the trial (baseline measurements) and four times at monthly intervals during the trial Serum triglycerides were determined twice in the baseline measurements and at the end of the 4-month study High density lipoprotein (HDL) cholesterol was measured immediately before and at the end of the treatment period

All blood measurements were carried out after an overnight fast Cholesterol and triglyceride concentrations were determined by an Autoanalyzer II apparatus (Technicon Instruments Tarrytown NY) using enzymatic assay (Boehringer Mannheim GmBH Germany) (9 14) HDL cholesterol was determined after precipitation of very low and low density lipoprotein with dextran sulphate manganese according to Kostner (3)

Statistical methods

Mean and S E M were calculated with a desk computer Mean values were compared with Student s *t* test Values expressed represent the mean ± S E M unless otherwise stated

RESULTS

The mean concentrations of serum cholesterol triglycerides and HDL cholesterol during the study are shown in Tables I and II Serum cholesterol decreased slightly in all three experimental groups during the 4-month observation period but the changes were not statistically significant The concentration of HDL cholesterol remained const[illegible] all groups A statistically significant decrea[illegible] serum triglycerides was seen in the subjects r[illegible] ing placebo whereas no changes were seen [illegible] other two groups

The effect of fiber administration on body [illegible] is shown in Fig 1 and Table III A consiste[illegible] highly significant decrease was seen in su[illegible] treated with guar gum whereas no change w[illegible] served in the other two groups The decre[illegible] body weight in group A was somewhat stee[illegible] obese subjects (relative b wt >115%) than i[illegible] viduals with normal body weight but the diff[illegible] was not statistically significant (data not sh[illegible] No correlation was found between the chan[illegible] body weight and serum lipids in any of the experimental groups

Gastrointestinal symptoms reported by th[illegible] ticipants in groups A and B during the stu[illegible] shown in Table IV Diarrhea gastric pai[illegible] flatulence were more frequent among the su[illegible] treated with guar gum than among those w[illegible] ceived placebo but the difference between th[illegible] groups was not significant

DISCUSSION

The results of this investigation indicate that addition of 15 g of guar gum to the Finnish diet not produce permanent changes in serum lip[illegible]

Table II *Serum triglyceride and HDL cholesterol concentrations (mmol/l) in groups A B and C a[illegible] beginning and end of the trial (mean ± S E M)*

Group	Triglycerides		HDL cholesterol	
	Before	At 4 mo	Before	At 4 mo
A (n=10)	1 84±0 24	1 79±0 25	1 69±0 13	1 69±0 12
B (n=11)	2 61±0 39	1 86±0 23*	1 41±0 15	1 50±0 14
C (n=11)	1 75±0 20	1 76±0 17	1 63±0 12	1 76±0 20

* The difference between initial and final values is significant ($p<0.05$ paired comparison)

Table III. *Body weight (kg) in groups A, B and C during the trial (mean ± S.E.M.)*

Group	Before treatment	Months after the beginning of treatment 1	2	3	4
(n=10)	62.9±2.1	61.3±2.1	61.2±2.1	61.3+2.2	60.4±2.2[a]
(n=11)	66.1±4.0	65.4±3.3	65.9±3.7	66.3+4.0	65.7±3.7
(n=11)	63.3±2.9	–	–	–	6? 7+2.9

[a] The difference between initial and final values is statistically significant ($p<0.0005$, paired comparison).

lipoproteins in female subjects with hypercholesterolemia. Lack of effect of guar gum on serum lipids is seemingly in disagreement with some earlier studies (5, 6). One explanation of the conflicting results might be the dose of guar gum. Thus, the amount of fiber used by us (15 g/day) is distinctly lower than the dose reported to reduce serum cholesterol in healthy males (36 g/day) (5). Also, in contrast to most of the previous investigations, all subjects in our study had hypercholesterolemia (IIA or IIB abnormality) and there is evidence to suggest that the response of normal and hypercholesterolemic subjects to diet and various hypolipidemic agents is not identical.

The most intriguing finding of our study was, however, the highly significant decrease in body weight observed in the guar gum group. Indirect evidence for the weight reducing properties of high fiber diet has earlier been obtained both from epidemiological surveys and animal experiments (4). Moreover, the few earlier studies conducted in human volunteers support the hypothesis that *abundant intake of fiber prevents excessive food* intake and induces loss of weight (2, 16). These observations are confirmed and extended by the results of the current double blind study: a highly significant weight reduction was seen in the guar gum group during the 4 month experiment, whereas no change was discernible in the two control groups.

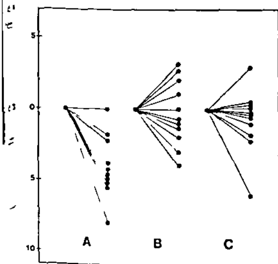


Fig. 1. Percentage change in body weight in the subjects of groups A (guar gum), B (placebo) and C (no medication) during the 4-month trial.

The mechanism behind weight reduction by dietary fibers is not clear. In general, diet rich in fiber has a lower calorie content and may also be less satiating than fiber depleted food. It has also been suggested that food fiber lowers caloric intake by promoting chewing and retarding the rate of food ingestion (4). These factors cannot, however, explain the present results, since the subjects took the fiber with a small amount of food or drink *before* meals. Thus, the most likely mechanism responsible for the weight loss is a decrease in the intestinal absorption of one or several components of the diet. In fact, fecal excretion of fatty acids has been reported to increase during diets supplemented with fiber (10, 15). Similarly, there is evidence that digestibility of protein is lowered by fiber (10). On the other hand, despite a significant retardation, the absorption of carbohydrates seems to be complete

Table IV. *Frequency (%) of reported gastrointestinal symptoms (flatulence, gastric pain and diarrhea) in groups A and B during the trial*

Group	Months after the beginning of treatment 1	2	3	4
A	80	60	50	60
B	36	72	36	45

even in the presence of large amounts of dietary fiber (6)

In summary our results indicate that the addition of 15 g of guar gum to the Finnish diet induces a significant weight loss in middle aged hypercholesterolemic females over a period of at least four months Despite the weight loss no significant changes were observed in blood lipids or lipoproteins in this patient group under the conditions applied It is suggested that regular ingestion of moderate amounts of fiber is a useful adjunct to the dietary therapy of obesity

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REFERENCES

1 Burkitt D Walker A R P & Painter N S Dietary fiber and disease JAMA 229 1068 1974
2 Evans E & Miller D S Bulking agents in the treatment of obesity Nutr Metab 18 199 1975
3 Fahrenbach M J Riccardi B A Saunders J C Lourie I M & Heider J G Comparative effects of guar gum and pectin on human serum cholesterol levels Circulation (Suppl) II 11 1965
4 Van Itallie T B Smith N S & Guartermain D Short term and long term components in the regulation of food intake Evidence of modulatory role of carbohydrate status Am J Clin Nutr 30 742 1977
5 Jenkins D J Leeds A R Newton C & Gu mings J H Effect of pectin guar gum and wh fibre on serum cholesterol Lancet 1 1116 1975
6 Jenkins D J A Wolever T M S Leeds A Gassull M A Haisman P Dilawari J Goff V Metz G L & Alberti K G Dietary fibres f analogues and glucose tolerance Importance of cosity Br Med J 1 1392 1978
7 Kelsay J L A review of research on effects of f intake on man Am J Clin Nutr 31 142 1978
8 Knox E G Foods and diseases Br J Prev Soc 1 31 71 1977
9 Röschlau P Bernt E & Gruber W Enzymat Bestimmung des Gesamt-Cholesterins im Serum Chem Klin Biochem 12 403 1974
10 Southgate D A & Durnin J V Cal factors An experimental reassessment of the used in the calculation of the energy value of diets Br J Nutr 24 517 1970
11 Trowell H Why a new term for dietary fiber? J Clin Nutr 25 926 1972
12 — Dietary fibre ischaemic heart disease and diab mellitus Proc Nutr Soc 32 151 1973
13 — Diabetes mellitus death-rates in England Wales 1920-70 and food supplies Lancet 2 998 1
14 Wahlefeld A W Triglycerides Determination enzymatic hydrolysis In Methods of enz analysis 2nd ed p 1831 Verlag Chemie and Academic Press New York and London 19
15 Walters R L Baird I M Davies P S Hill J Drasar B S Southgate D T Green Morgan B Effects of two types of dietary faecal steroid and lignin excretion Br Med J 2 1975
16 Yudkin J Diet and coronary thrombosis pothesis and fact Lancet 2 155 1957

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Hydralazine in Arterial Hypertension

Randomized Double Blind Comparison of Conventional/Slow Release Formulation and of b i d /q i d Dosage Regimens

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ABSTRACT Blood pressure (BP) control and tolerability of three two-week dosage regimens of hydralazine—conventional hydralazine q i d , conventional hydralazine b i d and slow release hydralazine b i d —were compared in a double blind randomized, cross-over trial in 20 out patients with arterial hypertension controlled with hydralazine in combination with other antihypertensive drugs The efficacy of the treatments was assessed during the last two days of each treatment period by determination of BP and pulse rate every hour between 8 a m and 6 p m No statistically significant differences in BP and pulse rate were found between the three treatment regimens, either in the variation during the day or in the mean value for the day There was a tendency to lowest BPs on conventional hydralazine q i d and to highest on conventional hydralazine b i d Mean differences in supine BP between conventional hydralazine b i d and slow release hydralazine b i d were 3 2 systolic and 0 5 mmHg diastolic In this short term study mean values with 95% confidence limits indicate that conventional hydralazine in a q i d dosage can be replaced by the same preparation or slow release formulation in a b i d dosage Acetylator phenotype was determined and had no significant influence on the results although there was a tendency to more widespread variability in systolic pressure and to a lower pulse rate in fast acetylators Unwanted effects were few and did not differ obviously between the treatments Whether the frequency of late toxicity of hydralazine is lower with slow release formulation remains to be evaluated in long term studies

Key words hydralazine slow release day curve of BP acetylator phenotype

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Poor patient compliance with antihypertensive drug regimens is well documented (1 15 40) The patients usually without symptoms have to follow a long term treatment schedule which may involve polypharmacy and frequent dose regimens both of which foster poor compliance Gatley (11) and Malahy (25) found that the number of drug defaulters increased with the frequency of doses and according to Ayd (3) over 80% of patients who were to take four or more drugs at least three times a day failed to take 25–60% of the prescribed dose of each whereas only 30% of those instructed to take one drug twice daily failed to take up to one fourth of the dose prescribed

Consequently a one or two-dose schedule has been introduced for β blocking agents such as propranolol (2) pindolol (10 14 18) metoprolol (34) and atenolol (26 42) Recently slow release formulations of propranolol (6 27) and oxprenolol (8 19 30) have become available for administration once a day

Hydralazine was introduced as a hypotensive agent in the early 50s Following the realisation that late toxicity with LED syndrome is dose related hydralazine in doses up to 200 mg daily has proved a valuable and efficient antihypertensive drug in combination with other preparations Since the introduction of β receptor blockers growing interest has been paid to the vasodilating effect of hydralazine as the combination with β-blockers prevents reflex tachycardia and hyperkinesia after hydralazine (22 36) It has been the practice to administer hydralazine in four doses per day as plasma half life is about three hours A simpler dosage regimen would be of great interest

The present investigation was undertaken to elucidate the following questions 1) Can hydralazine in the conventional formulation be administered b i d or is a q i d regimen necessary to control blood pressure? 2) Is a slow release formu

lation of hydralazine preferable to the conventional formulation? 3) Does the acetylator phenotype of the individual patient influence BP control?

METHODS AND PATIENTS

The trial

Using a double blind cross-over design hydralazine b.i.d (A) hydralazine q.i.d (B) and slow release hydralazine b.i.d (C) were compared for efficacy and tolerability. The trial comprised three two-week periods and the patients were randomized to one of the six treatment sequences ABC ACB BAC BCA CAB and CBA

Patients

Twenty out-patients (13 men 7 women) attending our Hypertension Clinic were included in and completed the trial. Their median age was 59.5 years (range 41–75) median height 170.5 cm (range 15–187) and median weight 77 kg (range 48–110). The median duration of antihypertensive treatment was 36 months (range 11–144) and the median duration of the pre trial treatment was 3.5 months (range 2–30)

The following criteria for inclusion were applied: hypertension according to WHO stage I or II of benign stable diastolic type and adequately controlled by a constant dose of hydralazine q.i.d in combination with a β-blocking agent and/or methyldopa as well as diuretics for at least two months. Excluded were patients with congestive heart disease valvular heart disease bradycardia with a heart rate at rest of less than 50 beats/min bronchospastic disorders renal insufficiency collagen disease insulin dependent diabetes mellitus and hypertensive retinopathy of grades III and IV

Medication

Double blind double-dummy technique was employed using tablets of identical appearance (Apresoline® 25 or 50 mg Apresoline® Retard 50 mg and placebo) delivered in weekly dispensers so that the number of doses and the appearance of the medication were constant during the three treatment periods. Tablets were taken at 8 a.m 1 6 and 10 p.m

Ten patients received 200 mg and ten 100 mg of hydralazine per day. Seventeen patients received either metoprolol or propranolol. Ten patients received methyldopa. The dose of concomitant medication was kept constant during the whole trial

Parameters

The patients were evaluated during the last two days of each of the three two-week periods. All efficacy criteria were recorded once an hour from 8 a.m until 6 p.m. They included systolic and diastolic BP supine and standing as well as pulse rate supine and standing. Korotkov sound phase V was used as the diastolic BP. The measurements were made by three observers (medical students) who were carefully instructed. A conventional sphygmomanometer was used with a cuff to suit the circumference of the arm

Tolerability was recorded on the first of the two d[...] evaluation

Routine laboratory tests (ESR hemoglobin le[...] creatinine alanine aminotransferases alkaline [...]phatases Na and K in serum) were performed b[...] allocation and at the end of each treatment period

Acetylator phenotype was determined in all [...] before entering the trial using the sulfadimidine m[...] (7). Ten patients were slow and nine fast acetylator[...] was slow/fast acetylator

Statistical methods

Parametric analysis of variance was used. The [...] treatments were compared for variation during the [...] well as for overall mean values of BPs and pulse rate[...] 11 supine BP values during the day in each period [...] based on means of 2×2 values i.e. two [...] every hour on two days. Similarly the standing [...] the pulse rate were based on means of 1×2 values [...] determination every hour on two days. The syst[...] variation between first and second supine BP me[...]ment on the same day was tested. The appropriate[...] using mean values was confirmed. The systematic [...]tions between the first and the second day's BP and [...] rate were also tested. Analyses based on the second [...] data compared to the means did not reveal any [...]ences

The assumption of homogeneity of variance held [...] data. Assumptions of normal distributions of data [...] not always met but violations were moderate and [...]ably unimportant

Tests for residual effects as well as period effect[...] made with the Koch (21) and Grizzle (13) models

For 11 patients all measurements were made [...] same observer for seven patients by two and f[...] patients by three observers. The variation due to [...] observers proved to be negligible (χ^2 test [...] analysis of variance and χ^2 goodness of fit on [...] digit preferences)

The BPs and pulse rates were tested for relations[...] the acetylator phenotype (parametric analysis of var[...] Bartlett's test). The statistical analysis was perform[...] B. Andersen

RESULTS

In no case were even non significant tende[...] towards either period effects or carry-over e[...] found

Supine blood pressure

Diurnal variation is shown in Fig. 1. No signifi[...] differences were found between the three tr[...]ments either for systolic or diastolic BPs (p>0.[...] though there was a non significant tendency [...] diastolic pressure to be lower late in the aftern[...] on hydralazine q.i.d. Significant variations d[...] the day were present on all three treatments w[...]

Table 1 *Supine blood pressure and pulse rate (mean values of 20 patients day means)*
hydralazine b i d B=hydralazine q i d C=slow release hydralazine b i d

	A	B	C	Differences of means A–B	A–C	C–B
–ood pressure (mmHg)						
ic						
Overall mean	175 2	169 5	171 9	5 7	3 2	2 5
S D	26 1	22 8	19 1			
Range	137 4–238 2	130 8–211 5	140 7–203 1	(−3 9–+15 3)	(−3 4–+9 9)	(−3 3–+8 2)
astolic						
Overall mean	98 2	97 1	97 7	1 0	0 5	0 5
S D	9 6	13 4	12 3			
Range	79 5–116 0	71 5–122 8	79 4–124 4	(−3 6–+5 6)	(−3 6–+4 5)	(−3.5–+4 5)
lse rate (beats/min)						
pine overall mean	64 9	65 1	64 7	−0 2 (−1 8–+1 3)	0 2 (−2 1–+2 5)	−0 4 (−2 3–+1 4)
anding overall mean	69 8	70 1	69 8	−0 2 (−2 1–+1 6)	0 0 (−2 4–+2 4)	−0 2 (−2 3–+1 9)

95% Confidence limits in parentheses

highest values in the morning and the evening ≤0 01)

The day means for supine BP are given in Table Although BPs were lower on hydralazine q i d an on the other two treatments the differences ere not statistically significant ($p \geq 0$ 10)

anding blood pressure

o statistically significant differences were found tween the three treatments either for diurnal var ion or for the day means ($p > 0$ 10)

stural blood pressure alteration

iere were no differences between the treatments >0 10) For systolic BP but not for diastolic re was a significant postural BP reduction <0 01)

pine and standing pulse rate

urnal variation is shown in Fig 2 No significant fferences were found between the three treat ents ($p \geq 0$ 10) Significant variations during the iy were found irrespective of treatment with in eased values after noon corresponding to the de ease in BP ($p < 0$ 01)

The day means for pulse rate are given in Table There were no significant differences between the atments ($p \geq 0$ 10)

Postural pulse rate alteration

There were no statistical differences between the treatments ($p \geq 0$ 10) and each was associated with a significant increase in pulse rate from supine to standing position ($p < 0$ 01)

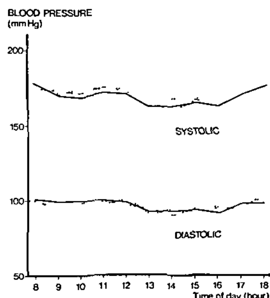


Fig 1 Diurnal variation of supine BP ($p > 0$ 10) = Hydralazine b i d — = hydralazine q i d — – slow re lease hydralazine b i d

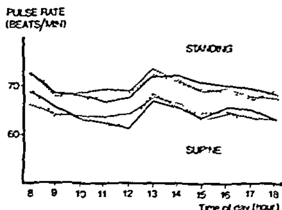


Fig 2 Diurnal variation of pulse rate ($p \geq 0\ 10$) Symbols as in Fig 1

Acetylator phenotype

There were no significant relationships in the treatments between acetylator phenotype and BPs or pulse rates in terms of diurnal variation or day means There was however a tendency for the variability of systolic pressure to be greater and pulse rate lower in fast acetylators

Tolerability

Three patients reported unwanted effects on conventional hydralazine One had chronic headache one had more sporadic headache and one had palpitations and tiredness The laboratory investigations did not show any notable differences during the trial

DISCUSSION

Hydralazine has a plasma half life of 2–3 hours (37) This has contributed to the current administration of four doses per day in the treatment of arterial hypertension Studies in rodents however indicate that hydralazine is rapidly taken up and retained by the arterial blood vessels but slowly released (20) Furthermore some metabolites of hydralazine are reported to be potent relaxants of vascular smooth muscle in vitro (28) There is consequently some basis for the experience that the antihypertensive effect lasts longer than one would expect from the plasma levels of the parent drug (28 38)

A few studies have compared two and four daily doses of hydralazine in conventional tablets O Malley et al (31) found identical BPs with b i d and q i d dosage regimens but the periods lasted only four days and only four patients were investigated

In a multicenter study of 153 patients (2[illegible] which included patients from smaller series ([illegible] no significant differences were found in BP or [illegible] rate but side-effects were more frequent on [illegible] than q i d dosage Some of the patients were [illegible] drawn from the b i d regimen due to inad[illegible] control of hypertension or side-effects All [illegible] above studies were performed in an open fas[illegible]

Other investigators (9 12 32) who [illegible] ried out comparative studies have found [illegible] quate antihypertensive effect of hyd[illegible] b i d dosage regimen

Present experience with the slow release [illegible] lation of hydralazine is limited The plasma [illegible] centration curve after single dose administ[illegible] *shows a lower peak compared with the conve[illegible]* al tablets (38 39 41) The maximum concent[illegible] is about 35% of that obtained with the conven[illegible] tablet and the peak appears after 1 5–3 [illegible] against 1–1 5 hours Conflicting results wer[illegible] tained by Henningsen (16) who observed a [illegible] peak with slow release tablets but this may [illegible] to the fact that his patients had renal insuff[illegible] or liver disease

Talseth et al (39) performed an open [illegible] which eight hypertensive patients prev[illegible] treated with conventional hydralazine q i d [illegible] crossed over to slow release hydralazine b i [illegible] identical daily doses There was no significa[illegible] ference in BP measured in the morning at mo[illegible] intervals although a small additional decrea[illegible] mean arterial BP was found The authors sugg[illegible] that this decrease might be due to improved p[illegible] compliance Henningsen (17) compared the [illegible] *hydralazine preparations in an open study* [illegible] patients and found no significant differences [illegible] and pulse rate between conventional tablets [illegible] 2–4 times daily and a slow release preparation [illegible] in either one or two daily doses

From this scant experience it is not possib[illegible] evaluate the role of slow release hydralazine [illegible] treatment of arterial hypertension The prese[illegible] vestigation was performed with a randomized [illegible] ble blind technique and furthermore BP [illegible] measured hourly for 11 hours on two days in [illegible] treatment period This yielded a total of 2640 [illegible] servations for each criterion Thus we obtaine[illegible] reliable estimate of BP regulation with conventi[illegible] hydralazine and slow release preparation resp[illegible] tively and the significance of two- or four-d[illegible] administration We found no statistically sign[illegible]

differences in either BP regulation or pulse rate for the two preparations in terms of variations during the day as well as means for the day but there was a tendency for BPs to be lower on conventional hydralazine q i d than on the other treatments Confidence limits indicate that it is unlikely that a switch from conventional hydralazine q i d to slow release or conventional formulation b i d will increase day means of systolic/diastolic BP by more than 8 2/4 5 and 15 3/5 6 mmHg respectively Similarly it is unlikely that BP will decrease by more than 3 3/3 5 and 3 9/3 6 mmHg respectively Whether this has clinical significance is a matter of judgement

Although the majority of patients show only insignificant differences in BP during the three treatments some patients may respond unacceptably to a change from a 4-dose to a 2-dose regimen On the other hand such a switch will probably improve BP control in some cases via better patient compliance The current investigation could not elucidate compliance because with the double dummy all patients received four daily doses

Side-effects are relevant to the value of hydralazine With the introduction of β adrenergic blockers as a basic treatment in combination with hydralazine the side effects caused by hyperkinesia are no longer a problem Side effects reported by our patients were so few as to lack importance The laboratory tests gave no indication of late toxicity but the study period is too short to elucidate this problem It is well known that the acetylator phenotype of the patient has some influence on the occurrence of late toxicity of hydralazine Thus hydralazine induced systemic lupus erythematosus occurs primarily in slow acetylators (4 33 35) and these patients have a higher concentration of hydralazine in plasma and a better BP control We therefore examined the acetylator phenotype in our patients with special reference to BP control and side effects No influence of the acetylator phenotype was found although there was a tendency to greater variability in systolic BP and a lower pulse rate in fast acetylators Whether the frequency of late toxicity of hydralazine will decrease with slow release formulation remains to be evaluated in long term studies

From our short term study we conclude that conventional hydralazine used q i d can in most patients be replaced by the same preparation or slow release preparation in b i d dosage without impairing BP control In a minority of patients however BP may increase unacceptably on a b i d regimen For these patients we recommend a four-dose scheme

REFERENCES

1 Åberg H Patient compliance Acta Med Scand (Suppl) 606 25 1977
2 Andersson O Berglund G Karlberg B Malmcrona R Olander R & Åberg H Propranolol i 2 dosprogram vid hypertoni Lakartidningen (Suppl) III 26 1972
3 Ayd F J Jr Single daily dose of antidepressants JAMA 230 263 1974
4 Boman G Hydralazine induced lupus reported to the Swedish Adverse Drug Reaction Committee In Symposium on Pharmacological and clin cal aspects of hydralazine (Apresoline®) in today s treatment of hypertension p 147 KA Trykk Oslo 1977
5 Cooper I Maintenance treatment of moderate hypertension with b i d hydralazine Curr Ther Res 20 579 1976
6 Douglas Jones A P Comparison of a once daily long acting formulation of propranolol with conventional propranolol given twice daily in patients with mild to moderate hypertension J Int Med Res 7 221 1979
7 Evans D A P An improved and simplified method of detecting the acetylator phenotype J Med Genet 6 405 1969
8 Forrest W A A multicentre evaluation of sustained release oxprenolol in the management of hypertension in hospital out patient practice J Int Med Res 6 136 1978
9 Freeman J B & Knight L W Oxprenolol and hydralazine in the treatment of hypertension Med J Aust (Special Suppl) 1 12 1975
10 Frithz G Pindolol i en dygnsdos vid hypertoni Lakartidningen 72 3073 1975
11 Gatley M S To be taken as directed J R Coll Gen Pract 16 39 1968
12 Goble A J Diuretics beta blockers and vasodilators dosage in m ld and moderate hypertension Med J Aust (Special Suppl) 1 14 1975
13 Grizzle J E The two-period change-over design and its use in clinical trials Biometrics 21 467 1965
14 Gyntelberg F Rasmussen K & Harvald B Antihypertensive treatment with pindolol in one or two doses Acta Med Scand 204 169 1978
15 Haynes R B Gibson E S Hackett B C Sackett D L Taylor D W Roberts R S & Johnson A L Improvement of medication compliance in uncontrolled hypertension Lancet I 1265 1976
16 Henningsen N C Hydralazine concentration as a tool in the aggressive treatment of hypertension In Symposium on Pharmacological and clinical aspects of hydralazine (Apresoline®) in today s treatment of hypertension p 188 KA Trykk Oslo 1977
17 — Maintenance of normotension in hypertensive middle aged men with a s ngle dosage of hydralazine

(Aprosoline* Retard) Paper presented at the VIIIth World Congress of Cardiology 17–23 Sept 1978 Tokyo Japan
18 Jacobsson K A Antihypertensiv terapi med pindolol – en jamförelse mellan två doser och en dos per dag Lakartidningen 73 2500 1976
19 Jones D H Reid J L Daniel J & Hamilton C A Double blind evaluation of single daily dosing with conventional and slow release oxprenolol Br J Clin Pract (Suppl) 1 12 1978
20 Keberle H Faigle J W Hedwall P Riess W & Wagner J Plasma concentrations and pharmacological response in animals In Biological efficacy of drugs in relation to their plasma concentrations (ed D S Davies & B N C Prichard) p 22 University Park Press Baltimore 1973
21 Koch G G The use of non parametric methods in the statistical analysis of the two period change-over design Biometrics 28 577 1972
22 Koch Weser J The comeback of hydralazine Am Heart J 95 1 1978
23 LeSher D A & Harris L Comparison of b i d vs q i d hydralazine dosage regimens in hypertensive patients on multiple drug therapy In Symposium on Pharmacological and clinical aspects of hydralazine (Apresoline*) in today s treatment of hypertension p 179 KA Trykk Oslo 1977
24 LeSher D A Harris L & Hawkinson R W Comparison of bid vs q i d hydralazine dosage regimens in hypertensive patients on multiple drug therapy Clin Pharmacol Ther 19 110 1976
25 Malahy B The effect of instruction and labeling on the number of medication errors made by patients at home Am J Hosp Pharm 23 283 1966
26 Marshal A J Barritt D W & Harry J D Dose response and frequency of administration of atenolol in essential hypertension—once daily treatment with beta blockade Postgrad Med J (Suppl) 3 168 1977
27 McAinsh J Baber N S Smith R & Young J Pharmacokinetic and pharmacodynamic studies with long acting propranolol Br J Clin Pharmacol 6 115 1978
28 McNay J L Haegele K D & McLean A J Duration of hydralazine action In Symposium on Pharmacological and clinical aspects of hydralazine (Apresoline*) in today s treatment of hypertension p 52 KA Trykk Oslo 1977
29 Myers S L & Myers C S Twice daily treatment with hydralazine Clin Med 84 19 1977
30 Newton M Slow oxprenolol in hypertension Clin Pract (Suppl) 1 8 1978
31 O Malley K Segal J L Israili Z H Boles McNay J L & Dayton P G Duration of hy azine action in hypertension Clin Pharmacol 18 581 1975
32 Pape J F Pytte R & Fauchald P Langt handling av essensiell hypertensjon med hydr og alprenolol Tidsskr Nor Lægeforen 98 55? 1
33 Perry H M Jr Tan E M Carmody Sakamoto A Relationship of acetyl transfera tivity to antinuclear antibodies and toxic sympto hypertensive patients treated with hydralazine Clin Med 76 114 1970
34 Raybrouck T Amery A Fagard R Jouste Lijnen P & Meulepas E Beta blockers on three times a day? Br Med J I 1386 1978
35 Strandberg I Boman G Hassler L & Sjo F Acetylator phenotype in patients with dralazine induced lupoid syndrome Acta Med 200 367 1976
36 Symposium on Pharmacological and clinical as of hydralazine (Apresoline*) in today s treatm hypertension KA Trykk Oslo 1977
37 Talseth T Studies on hydralazine I Serum centrations of hydralazine in man after a single and at steady state Eur J Clin Pharmacol 1(1976
38 — Serum concentrations of hydralazine during ment with conventional and slow release tablet Symposium on Pharmacological and clinical as of hydralazine (Apresoline*) in today s treatm hypertension p 88 KA Trykk Oslo 1977
39 Talseth T Fauchald P & Pape J F Hydral slow release observations on serum profile and cal efficacy in man Curr Ther Res 21 157 1977
40 Taylor D W Sackett D L Haynes R Johnson A L Gibson E S & Roberts R Compliance with antihypertensive drug therapy NY Acad Sci 304 390 1978
41 Wagner J In Symposium on Pharmacologica clinical aspects of hydralazine (Apresoline*) i day s treatment of hypertension p 112 KA Tr Oslo 1977
42 Zacharias F J Hayes P J & Cruickshank J Atenolol in hypertension a double blind compa of the response to three different doses Postgrad J (Suppl) 3 114 1977

QT_c Intervals at Discharge after Acute Myocardial Infarction and Long-Term Prognosis

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ABSTRACT QT_c intervals were measured retrospectively in 463 survivors of AMI with a mean age of 65 years The measurement was made once at discharge from hospital Patients with anterior infarcts had significantly longer QT_c intervals than those with inferior or uncertain infact localization A weak but significant correlation was found between S-GOT maximum and QT_c interval Patients with ventricular arrhythmias in the CCU had longer QT_c intervals Patients with a poor long term prognosis had significantly shorter QT_c intervals This finding was explained by digitalis therapy Among patients without bundle branch block, digitalis and quinidine, those below 66 years of age who died within the first 24 months tended to have longer QT_c intervals than the survivors It is concluded that measurements of QT_c interval at discharge have no long term predictive value This factor may, however, have some bearing on the short term prognosis in younger patients without therapy which affects the QT_c interval

Key words QT interval acute myocardial infarction prognosis

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Prolongation of the corrected QT (QT_c) interval may be associated with an imbalance of the sympathetic nervous system (22 24 29) cardiac disease (26) electrolyte disturbance (16 27) and drug therapy (19) Ventricular fibrillation (VF) and sudden death have been described in two congenital syndromes with QT_c prolongation (15 20 23 28) Recently studies have appeared on QT_c intervals in patients with ischemic heart disease (IHD) Patients with acute myocardial infarction (AMI) showed QT_c interval prolongation during the acute phase in two investigations (1 8) A relationship between QT prolongation measured in the first ECG on admission to a coronary care unit (CCU) and malignant ventricular arrhythmias during the CCU stay seems to exist in patients with AMI (2) Furthermore survivors of out-of hospital VF with coronary heart disease have been shown to have longer QT_c intervals than ambulatory post MI patients without VF (10) and survivors of MI with a constant QT_c interval prolongation have been reported to be at high risk of sudden death (25)

The aim of this retrospective investigation was to study the QT_c interval at discharge after an AMI and to evaluate its clinical and long term prognostic implications

PATIENTS AND METHODS

From 1968 to 1970 475 patients with AMI were treated in the CCU at Serafimerlasarettet and discharged alive The routines of the unit criteria for admission and diagnosis as well as a description of the patient group have been published earlier (6 12) Previous diseases physical findings ECG signs as well as complications in the CCU were registered on special charts and transferred to punch cards for computer analysis (9)

Three patients who had pacemakers and nine who could not be traced at the follow up in Dec 1973 were excluded The study thus included 463 patients 304 men (66%) and 159 women (34%) with a mean age of 65 years (range 39-93)

Patients without bundle branch block (BBB) digitalis or quinidine therapy—factors known to influence the QT interval (16)—were studied separately These 210 patients will be referred to below as the subgroup

The mortality was evaluated on Dec 31 1973 3-6 years after admission for the index infarction Classification of modes and causes of death was based upon data from death certificates and hospital records The routine police records of patients who had died outside hospital were checked for relevant information

The QT interval was measured on the ECG recorded at

Abbreviations QT =corrected QT interval MI=myocardial infarction AMI acute MI VF ventricular fibrillation IHD=ischemic heart disease CCU=coronary care unit BBB=bundle branch block VEBs=ventricular ectopic beats VT=ventricular tachycardia

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Table I *Mean QT_c (sec) at discharge in relation to previous diseases*

	All patients (n=463)			Subgroup (n=210)		
Previous diseases	%	Mean QT_c	p	%	Mean QT_c	p
MI	24	0 426	NS	18	0 428	NS
No MI	76	0 426		82	0 431	
Angina pectoris	61	0 425	NS	57	0 429	NS
No angina pectoris	39	0 430		43	0 435	
Heart failure	29	0 414	<0 001	12	0 424	NS
No heart failure	71	0 432		88	0 432	
Hypertension	30	0 428	NS	20	0 435	NS
No hypertension	70	0 426		80	0 429	

discharge usually towards the end of the third week From a 12 lead resting ECG at a speed of 50 mm/sec the QT and RR intervals were measured in 3–5 consecutive beats The values were averaged and QT was calculated from the mean value according to Bazett s formula (5 16)

$$QT_c = \frac{QT}{\sqrt{RR}}$$

The measurement was made in the ECG lead with the longest QT interval Care was taken not to measure QT intervals preceded by premature beats or to include U waves in the QT interval The QT interval was measured in hundredths of a second from the beginning of the QRS complex to the end of the T wave where its hind limb joined the base line Differentiation between T and U waves or some other potential was usually possible in at least one lead If this was not possible the QT interval was measured from the beginning of the QRS complex to the notch between the T and U waves (16) All measurements were made by one of us (S A) without knowledge of the patients clinical data

Definitions

Previous myocardial infarction was accepted when reported by a patient and preferably verified by hospital records or ECG findings *Previous heart failure* a history of digitalis therapy or diuretic therapy not given for hypertension *Hypertension* a history of high blood pressure treated with antihypertensive agents *Acute myocardial infarction and angina pectoris* were diagnosed according to conventional criteria (12 21) *Left heart failure* was diagnosed by the presence of basal pulmonary rales or pulmonary vascular congestion on X ray *Site of infarct* anterior if the ECG criteria for infarction were present in two or more of leads CR $_5$ lateral if in two or more of leads I aVL CR_6 and CR_7 and inferior if in two or more of leads II III and aVF Combination sites were determined according to the same criteria In the following presentation ECGs with anterolateral sites were classified as anterior and inferolateral as inferior Combined locations included antero (lateral) inferior infarcts ECGs with signs of subendocardial infarcts or with BBB were classified as equivocal *Sudden death* was defined as death within 2 hours after onset of the final symptoms

Statistical methods

Conventional statistical methods were used The si[illegible] cance of differences between the QT_c of each p[illegible] group was tested by Student s t test

RESULTS

Clinical Features in Relation to QT_c at Disch

Age sex and previous diseases

QT_c intervals were not significantly related to or sex either in the entire patient group or i[illegible] subgroup and were not longer in patients with [illegible]vious MI angina pectoris or hypertension [illegible]ever patients with a history of heart failure significantly shorter QT_c intervals than the [illegible]der This difference was not noted in the subg[illegible] (Table I)

Infarct site size and complications

Patients with anterior infarcts had significa[illegible] longer QT_c intervals than those with inferior [illegible]farcts or infarcts of uncertain localization This true also in the subgroup (Table II)

Patients with high S-GOT maximum (normal [illegible]ue <40 U/l) had significantly longer QT_c inter[illegible] than those with lower values (Table III) an[illegible] similar non significant tendency was registered the subgroup This is also reflected by a weak significant correlation between S GOT maxim[illegible] and QT_c intervals (r=0 13 p<0 01) in the en[illegible] patient group Patients with anterior infarcts [illegible] significantly higher S GOT mean values than th[illegible] with uncertain site of the infarct (p<0 001) [illegible] such difference existed between patients with a[illegible]terior and inferior infarcts either in the total pati[illegible] group or in the subgroup

ble II *Mean QT_c (sec) at discharge in relation to site of index infarct*

of infarct	All patients (n=463) %	Mean QT	Subgroup (n=210) %	Mean QT_c
terior or anterolateral	32	0 437 } ** } ***	34	0 445 } *** } *
erior or inferolateral	25	0 424	36	0 419
teral	4	0 438	6	0 433 } *
mbined	3	0 424	3	0 446
certain	35	0 417	21	0 426

$p<0.05$ ** $p<0.01$ *** $p<0.001$

QT_c intervals in patients with signs of heart fail e in the CCU did not differ from those in patients thout heart failure There was no relationship tween heart size measured by chest X ray at dis arge and QT_c interval

Patients with ventricular ectopic beats (VEBs) in CCU had significantly longer QT_c intervals than others (Table III) Patients with ventricular chycardia (VT) (≥3 VEBs in succession) also had gnificantly longer QT_c intervals Nine patients id developed VF in the CCU Their QT_c was 439±0 037 sec (mean±S D) and somewhat nger than the QT_c of patients with VT but it did it differ significantly from that of the remainder 426±0 043 sec)

undle branch block digitalis and quinidine therapy

he mean QT_c of the 210 patients in the subgroup without BBB digitalis or quinidine was 431±0 034 sec Nine patients had BBB but were it on digitalis or quinidine Their QT_c was 472±0 039 sec and differed significantly from that the subgroup ($p<0.001$) Fifty three patients ere treated with quinidine but had neither BBB nor gitalis therapy Their mean QT was 0 454±0 047 sec and significantly prolonged (5%) compared with the subgroup ($p<0.001$) A large number of patients were on digitalis ($n=152$) but they did not have BBB or quinidine therapy Their mean QT_c was signifi cantly shorter (6%) than that of the subgroup (0 403±0 039 vs 0 431±0 034 sec $p<0.001$) No significant difference in any of the parameters presented in Tables I–IV was found among the digitalis treated patients Regarding all these pa rameters the patients on digitalis had significant ly shorter QT_c intervals than those in the subgroup

Follow up

During the follow up period 177 patients (38%) died Their mean age at death was 69 years (range 45–93) The mean QT_c at discharge of the 286 sur vivors was 0 431±0 043 sec significantly longer than that of the non survivors 0 419±0 042 sec ($p<0.01$) (Table IV) Almost identical values were however noted between survivors and non sur vivors in the subgroup (Table IV)

Of the 286 survivors 41 were on quinidine only (mean QT_c 0 454±0 044 sec) and eight on both digitalis and quinidine (mean QT_c 0 426±0 029 sec) Fifty three patients (19%) were on digitalis

ible III *Mean QT_c (sec) at discharge in relation to S GOT_{max} and complications during the CCU period*

	All patients (n=463) %	Mean QT	p	Subgroup (n=210) %	Mean QT	p
GOT_{max} <200 μ/l	77	0 423	<0 01	80	0 429	NS
GOT_m >200 μ/l	23	0 436		20	0 439	
ft heart failure	67	0 427	NS	54	0 432	NS
o left heart failure	33	0 424		46	0 429	
EBs	87	0 429	<0 01	86	0 433	<0 01
o VEBs	13	0 410		14	0 416	
T	40	0 434	<0 01	36	0 435	N S
o VT	60	0 421		64	0 428	

Table IV *Mean QT_c (sec) at discharge in relation to survival and different modes of death during the follow up*

	All patients (n=463)				Subgroup (n=210)	
	%	Mean QT			%	Mean QT
Survivors	62	0 431	**		78	0 431
Deceased	38	0 419			22	0 430
Mode of death						
Sudden <2 h	7	0 424	*	**	5	0 420
IHD 2–2 h	8	0 424			5	0 444
IHD >24 h	13	0 413			8	0 428
Not IHD	9	0 414			5	0 427

* $p<0.05$ ** $p<0.01$

only and had significantly shorter intervals than the other survivors (mean QT_c 0 403±0 043 vs 0 437±0 041 sec $p<0.001$)

Twelve of the 177 patients who died were on quinidine only (mean QT_c 0 452±0 045 sec) and ten on both digitalis and quinidine (mean QT_c 0 421±0 043 sec) Ninety three (53%) of those who died were on digitalis only Their mean QT_c was significantly shorter than that of the other non survivors (0 403±0 039 vs 0 437±0 041 sec $p<0.001$)

The relation between QT_c interval and mode of death is shown in Table IV Sixty nine patients (15%) died of IHD within 24 hours after onset of the final symptoms Their mean QT_c value did not differ significantly from those who died of IHD 24 hours or more after onset of symptoms or from those who died from other causes than IHD Forty nine patients (11%) died within six months 28 (6%) 7–12 months and 100 (22%) more than 12 months after discharge These three groups of deaths did not differ significantly as to their mean QT_c intervals nor were any differences found within these groups when QT_c intervals were related to the mode of death Separate analysis of the subgroup also failed to show any relationship between QT_c interval and time and mode of death

However among patients below 66 years of age (n=237) those who suffered a cardiac death within the first follow up year (n=21) tended to have longer QT_c intervals than the survivors (0 432±0 044 vs 0 427±0 040 sec N S) This tendency was also found when only cardiac deaths (n=14) during the first six months were considered (0 434±0 041 vs 0 426±0 040 sec N S) Among subgroup patients below 66 years of age (n=139) the difference in QT_c interval between those died within six months after discharge (n=7) the survivors reached an almost significant l (0 440±0 042 vs 0 427±0 032 sec) Analysis these two groups below 66 years regarding parameters presented in Tables I II and III show the same tendencies as in the corresponding gr without age limit

VT had been registered in 185 patients in CCU 123 (66%) of them survived the follow period and their QT_c value was 0 436±0 sec compared to 0 431±0 046 sec in 62 patients VT who died There was no association QT_c interval and time and mode of death in group However three of the subgroup pati with VT who died within the first six mo had prolonged QT_c intervals (0 483±0 040 0 433±0 037 sec $p<0.05$)

A QT_c interval of 0 440 sec is often used a normal upper limit (21) 143 (31%) of our pat had QT_c intervals exceeding this value A QT terval above 0 440 sec was not associated wit increased mortality

DISCUSSION

Simple methods to identify high risk patients an AMI are needed for intervention studies report presents the long term prognostic imp tion of QT_c at discharge from hospital So far study of Schwartz and Wolf (25) in which repe QT_c measurements were performed during a en year follow up in 55 post MI patients is only one reporting a prognostic significance of longed QT_c intervals in survivors of AMI The thors who did not include patients with BBE digitalis induced changes that obscured the E analysis in their study population found that 28 patients who died all of them suddenly significantly longer QT_c intervals than the surviv and the matched controls Contrary to their resu we found that patients who died had significar shorter QT_c intervals than the survivors This explained by the digitalis therapy in this group patients with congestive heart failure and acco ingly poor prognosis This finding of drug influe on QT_c points to the difficulty in using this inter in prognostication Schwartz and Wolf did not d cuss in detail possible drug influence on QT_c the other hand the influence of drugs may ha

een less important in their fairly young patient group (mean age 52 years)

More in agreement with the findings of Schwartz and Wolf our patients below 66 years of age who died within the first follow up year and especially those who died in the first six months had a tendency to longer QT_c intervals at discharge than the corresponding survivors This was even more marked in patients without BBB or digitalis and quinidine treatment In another study in which the same age selection was used (1) we found an association between prolonged QT_c intervals at discharge and reinfarction and sudden death in survivors of AMI In that study we measured QT_c intervals on several occasions during the follow up period It is possible that a constant QT_c prolongation increases the prognostic weight of this parameter since patients with normal mean QT_c (below 0.44 sec) occasionally had a prolonged QT_c interval which was found also by Schwartz and Wolf

QT_c prolongation during the acute phase of AMI has recently been reported (1 8) On the contrary our report deals with the measurement of QT_c interval during the subacute phase of AMI Our findings indicate that a history of previous MI does not influence the QT_c interval after AMI in contrast to the extent of myocardial damage during the recent AMI Thus we found a weak correlation between S-GOT maximum and QT_c at discharge This does not agree with the results of Doroghazi and Childers (3) who found no association between peak creatine kinase values and the presence of transient QT_c lengthening beyond the normal limit during the hospital stay in patients with AMI From our results it is obvious that there are other factors which influence the QT_c interval as our patients with anterior infarcts had longer QT_c intervals than those with inferior infarcts though there was no significant difference between them in S-GOT maximum The causes and implications of this finding are uncertain The difference might to some extent be explained by the method of ECG registration with more extensive changes in the precordial leads facing the anterior wall of the left ventricle than in the standard leads reflecting the inferior one

Prolongation of the QT_c interval is sometimes seen in patients with the billowing mitral valve syndrome (3 4 18) and may be of relevance to its association with malignant ventricular arrhythmias and sudden death (26) This relationship between QT_c prolongation and malignant ventricular arrhythmias also exists in certain hereditary syndromes (15 20 28) Our patients with ventricular arrhythmias during the CCU stay had longer QT_c intervals at discharge from hospital than those without these arrhythmias In patients with all forms of VEBs including VT and VF this difference was not explained by the effect of therapy This association between QT_c prolongation and ventricular arrhythmias in patients with IHD is also reflected by the report of Haynes et al (10) who found repolarization abnormalities including QT_c prolongation in survivors of out-of hospital VF In a previous study we found an association between QT_c prolongation on admission in patients with AMI and malignant ventricular arrhythmias during the acute phase (2)

Other factors previously found to be related to changes in QT_c include hypertension (11 16) but no such relationship was evident in our patients It may be that the recent infarction had a dominant influence on the QT_c interval (1 8) In contrast to the findings of Hegglin and Holzmann (11) prior heart failure was related to a short QT_c interval in our patients This may be explained by the shortening effect of digitalis on QT_c However at discharge most patients who had shown signs of heart failure in the CCU were not on digitalis but on diuretics alone These drugs will not influence the QT_c interval unless electrolyte disturbances are induced (27) and no patient showed such imbalance at the time of discharge

The present findings indicate that the QT_c interval measured at discharge from hospital is associated with the extent of the recent myocardial damage the site of the infarct and ventricular ectopic activity during the CCU period Our data also indicate that the QT_c interval as such measured once in the subacute phase of the illness hardly has any bearing on the long term prognosis We found that drug therapy—in this study digitalis—interferes to a considerable extent with the evaluation of QT_c as a prognostic indicator There was however a tendency to QT_c interval prolongation in younger patients not on drugs affecting QT_c and without BBB dying within the first half year after their AMI Several studies have pointed to the feasibility of estimating prognosis after an AMI (7 12 17) However a number of patients dying early after discharge carry none of the ordinary unfavourable prognostic signs (14) This warrants a search for new prognostic factors that may increase our pre-

dictive ability It has been suggested that repeated assessments of a prognostic factor may improve their predictive value (13) This has been done with QT_c interval by Schwartz and Wolf (25) with promising results The prognostic implications of the QT_c time in combination with other prognostic factors remain to be evaluated and will be discussed in a further report

ACKNOWLEDGEMENT

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REFERENCES

1. Ahnve S Lundman T Helmers C & Rehnqvist N Q-T interval as a prognostic factor after acute myocardial infarction 8th World Congress of Cardiology Tokyo Japan 1 150 1978
2. Ahnve S Lundman T & Shoaleh var M The relationship between QT interval and ventricular arrhythmias in acute myocardial infarction Acta Med Scand 204 17 1978
3. Barlow J B Conjoint clinic on the clinical significance of late systolic murmurs and non-ejection systolic clicks J Chron Dis 18 665 1965
4. Barlow J B Pocock W A Marchand P & Denny M The significance of late systolic murmurs Am Heart J 66 443 1963
5. Bazett H C An analysis of the time relations of electrocardiograms Heart 7 353 1920
6. Biorck G Lundman T Mogensen L & Orinius E Experience from a coronary care unit Arch Klin Med 216 242 1969
7. Coronary Drug Project Research Group Factors influencing long term prognosis after recovery from myocardial infarction—three year findings in the Coronary Drug Project J Chronic Dis 27 267 1974
8. Doroghazi R M & Childers R Time related changes in the Q-T interval in acute myocardial infarction Possible relation to local hypocalcemia Am J Cardiol 41 684 1978
9. Hall P Lundman T & Nordlander R Computerized case records in a cardiac infarction ward Lakartidningen 70 4305 1973
10. Haynes R E Hallstrom A P & Cobb L A Repolarization abnormalities in survivors of out-of hospital ventricular fibrillation Circulation 57 654 1978
11. Hegglin R & Holzmann M Die klinische Bedeutung der verlangerten QT Distanz (Systolendauer) im Elektrokardiogramm Z Klin Med 132 1 1937
12. Helmers C Short and long term prognostic indices in acute myocardial infarction Acta Med Sc (Suppl) 555 1974
13. — Aspects on prognostication in myocardial infarction Eur J Cardiol 10 1 1979
14. Helmers C & Lundman T Early and sudden deaths after myocardial infarction Acta Med Sc 205 3 1979
15. Jervell A & Lange Nielsen F Congenital deaf mutism functional heart disease with prolongation of the QT interval and sudden death Am Heart J 54 1957
16. Lepeschkin E Modern electrocardiography vol Williams & Wilkins Baltimore 1951
17. Moss A J DeCamilla J Davis H & Bayer The early post hospital phase of myocardial infarction Circulation 54 58 1976
18. Reid J V O Mid systolic clicks S Afr M 35 353 1961
19. Reynolds E W & Vander Ark C R Quinidine syncope and the delay repolarization syndrome Mod Concepts Cardiovasc Dis 45 117 1976
20. Romano C Gemme G & Pongiglione R Aritmie cardiache rare dell età pediatrica II Accessi sincopali per fibillazione ventricolare parossistica Pediatr 45 656 1963
21. Rose G & Blackburn H Cardiovascular survey methods WHO Geneva 1968
22. Schamroth L The disorders of cardiac rhythm 135 and 177 Blackwell Scientific Publications Ox 1971
23. Schwartz P J Periti M & Malliani A The long Q-T syndrome Am Heart J 89 378 1975
24. Schwartz P J & Stone H L Role of right stellate ganglion during exercise Eur J Clin Invest 6 1976
25. Schwartz P J & Wolf S Q-T interval prolongation as predictor of sudden death in patients with myocardial infarction Circulation 57 1074 1978
26. Shappell S D Marshall C E Brown R E & Bruce T A Sudden death and the familial occurrence of mid systolic click late systolic murmur syndrome Circulation 48 1128 1973
27. Surawicz B Electrolytes and the electrocardiogram Mod Concepts Cardiovasc Dis 33 875 1964
28. Ward O C A new familial cardiac syndrome in children J Irish Med Ass 54 103 1964
29. Yanowitz F Preston J B & Abildskov J A Functional distribution of right and left stellate innervation to the ventricles Production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone Circ Res 18 416 1966

Antiarrhythmic Properties of a Neuroleptic Butyrophenone, Melperone, in Acute Myocardial Infarction

A Double Blind Trial

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ABSTRACT In vitro animal studies suggest melperone, a neuroleptic butyrophenone, to be a type III antiarrhythmic drug according to the classification of Vaughan Williams It has no negative inotropic effect on cardiac muscle A double-blind trial of 3 hours duration was carried out with melperone and placebo in 26 patients admitted to the CCU with suspected acute myocardial infarction (AMI) and ventricular arrhythmias Melperone, 50 mg i v was superior to placebo in reducing the total number of ventricular ectopic beats (VEB) as well as the number of minutes with either frequent, multifocal, R on T type or runs of VEB The reduction became statistically significant in the second treatment hour in patients with definite AMI Melperone induced sedation and reduction of systemic BP in most of the patients Two patients with low initial systolic BP achieved a further reduction and had BP levels below 90 mmHg Two experienced minor side-effects In conclusion melperone administered in large i v doses to patients with AMI induced sedation acute BP reduction and some reduction of ventricular arrhythmia

Key words myocardial infarction arrhythmia neuroleptic continuous ECG

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The high incidence of ischemic heart disease makes it necessary to search for neuroleptics (major tranquilizers) without harmful side-effects on the heart and circulation Melperone is a neuroleptic butyrophenone which differs from high-dose neuroleptics of the phenothiazine type in having no anticholinergic effect (2) Studies on isolated guinea pig papillary muscles have shown differences among neuroleptics concerning their influence on the action potential Only melperone prolongs the action potential without affecting the contractile force (1) This indicates antiarrhythmic properties of type III according to the classification of Vaughan Williams (11)

In a preliminary unpublished study melperone given i v to patients suffering from acute myocardial infarction (AMI) was well tolerated and seemed to reduce the number of ventricular ectopic beats (VEB) when doses exceeded 20 mg In the present study the VEB reducing effect of melperone is evaluated against that of placebo in patients with suspected AMI and ventricular arrhythmias

PATIENTS AND METHODS

Twenty three males and three females admitted to the Coronary Care Unit (CCU) with suspected AMI entered this study Table I gives relevant data for the entire series Myocardial infarction was diagnosed according to the WHO criteria (12) in 16 patients 10 were assigned to the non-infarction group

Ventricular arrhythmia was defined according to the following criteria *VEB* Premature QRS complex with a duration of more than 0 10 sec and a configuration different from the regular QRS complex *Monofocal VEB* VEB of similar configuration and constant coupling time to the normal complex *Multifocal VEB* VEB of different configurations *R-on T type VEB* VEB starting in a T wave *Runs of VEB* 2–5 VEB in succession with a frequency of more than 100 beats/min *Ventricular tachycardia (VT)* More than 5 VEB in succession with a frequency of more than 100 beats/min The criteria for entering the trial were frequent VEB (more than 5 VEB/min) and/or multifocal VEB and/or runs of VEB and/or R-on T type VEB

Abbreviations AMI = acute myocardial infarction BP = blood pressure VEB = ventricular ectopic beats VT = ventricular tachycardia VF = ventricular fibrillation CCU = coronary care unit

Table I *Distribution of patients completing the trial*

	Proven AMI		Non proven AMI	
	Melperone	Placebo	Melperone	Placebo
No of pats	9	5	5	5
Sex				
♂	8	3	5	5
♀	1	2	0	0
Age (y)				
Mean	66	67	68	66
Range	56–73	49–84	54–85	56–78
Infarction site				
Anterior	5	4		
Posterior	3	1		
Uncertain or combined	1	0		
Duration of symptoms before study				
<4 h	0	1		
4–24 h	4	3		
>24 h	5	1		
Cardiac enlargement (chest X-ray)	7	3	3	3
Pulmonary congestion (stethoscopic)	5	2	2	1
Previous myocardial infarction	1	1	4	3
Digoxin treated	1	3	1	3
Atrial fibrillation	1	1	0	0

Patients with VT systolic blood pressure (BP) below 90 mmHg frank pulmonary edema or bradycardia (heart rate below 50 beats/min) or any degree of sinoatrial or atrio ventricular block were excluded

All patients were ECG monitored continuously for 3 hours during their stay in the CCU (Fig 1) The ECG recordings were performed with a Mingograph 61 (paper speed 10 mm/sec) connected to the central monitoring equipment using the same precordial lead and out of sight of the patient The first hour served as a reference and no treatment was given Heart rate systemic BP by the cuff method respiratory rate and general clinical condition were recorded One hour after the start of the ECG monitoring 50 mg of either melperone (Buronil®) or placebo (solvent alone) in a 10-ml injection in five divided doses were given every other min during a 10-min period After each injection heart rate BP respiratory rate and general condition were re recorded During the next two hours the patients were re-examined and interviewed according to a questionnaire regarding side-effects The 180-min ECG strips were analysed blindly by manual counting of the ventricular arrhythmias according to the definitions

Statistical analyses were made by Student s *t* test with the significance level chosen as $p<0.05$

RESULTS

The results are presented in Tables II and III

In patients with AMI receiving melperone number of minutes with ventricular arrhyt (either frequent multifocal R on T type or ru VEB) was significantly reduced in the second treatment hour Furthermore melperone prod a significant reduction of the most common type of arrhythmia (i e frequent VEB) Placebo not alter significantly the frequency of arrhyth in the AMI group The frequency of arrhythm the non infarction group seemed rather const being equally influenced by melperone and place

Two patients with AMI one receiving mel perone and the other placebo were excluded du short lasting VT None of the patients develo ventricular fibrillation (VF) No sort of block sinoatrial atrioventricular or bundle branch blo developed during melperone treatment Two tients received submaximal doses of melpero

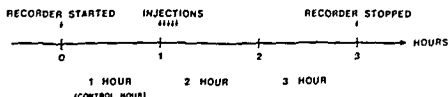


Fig 1 Schedule of the tr

able II *Overall arrhythmia frequency (mean ±S E M)*

he first hour served as a control hour after which the injections were given The arrhythmias were analysed manually lue to the different mean control values for melperone and placebo for patients with AMI the statistical evaluation student s t test) was performed as an intra-group and not a between-group comparison

	Proven AMI		Non proven AMI	
	Melperone (N=9)	Placebo (N=5)	Melperone (N=5)	Placebo (N=5)
linutes with >5 VEB				
1st h	37 3±4 8	26 8± 6 6	23 8±11 1	30 0+10 6
2nd h	22 7±6 8	18 4± 8 8	15 5± 8 9	27 6+10 9
3rd h	15 4±6 4*	14 4±10 1	21 6±11 0	25 0±11 9
linutes with either >5 VEB nultifocal VEB run of VEB or R/T				
1st h	39 0±4 8	30 8± 6 3	30 0±11 0	38 0+ 9 8
2nd h	24 7±6 4	22 2± 8 0	26 8± 9 9	35 6±11 8
3rd h	16 6±6 4*	16 4± 9 3	25 8±11 4	31 4±12 7
EB (%)				
1st h	11 4±2 1	7 6± 2 9	7 9± 3 9	7 4± 3 0
2nd h	6 0±1 5	5 1± 2 3	7 5± 4 4	7 0± 3 1
3rd h	5 5±2 5	5 8± 4 3	7 8± 4 4	7 3± 3 4

$p \leq 0.01$

0 and 40 mg) due to decreasing systolic BP from 0 to values below 90 mmHg Melperone reduced gnificantly the systolic and diastolic BP No sig ficant change was found in the heart rate (Table I)

Of the melperone treated patients 11 were ited with maximum effect in the second post eatment hour and only 4 felt unchanged Of the acebo-treated patients 9 felt unchanged and 2 xperienced some drowsiness Two melperone eated patients complained of dizziness one ex erienced dryness of the mouth and one complained bout a general feeling of warmth Otherwise no de-effects were recorded in either group

Table III *Changes in heart rate and BP from be ore injections to after the last injection 10 min later mean ±S D)*

	Changes in heart rate (beats/min)	Changes in BP (mmHg)	
		Systolic	Diastolic
elperone N=15)	1 7±10	−15 3±13 1	−6 7±12 1
acebo N=11)	0.5±10	1 8±4 1	4 1±7 4
value	0 77 (NS)	<0 001	0 02

DISCUSSION

Since the late 60s certain ventricular arrhythmias have been considered as warning signals of primary VF in myocardial infarction (7) It has been gener ally accepted that these arrhythmias should be treated in order to prevent VT and VF However some investigators found that 50% of all primary VFs occur without warning arrhythmias (4 5 6) Therefore studies on antiarrhythmic drugs should concentrate on the prophylaxis of VF in all patients suspected of AMI

We tried to evaluate the effect of melperone on warning arrhythmias Even well trained nurses de tect only a small fraction of ventricular arrhythmias on a monitor scope (8) Computer based arrhythmia detection is also associated with serious drawbacks (3) Therefore we used manual evaluation of con tinuously recorded paper ECG during a 3 hour period

Due to the variation in occurrence of arrhythmia in intermittent ECG sampling (Fig 2 and ref 10) we decided to use a 60-min period as control before treatment Since VT must be considered a real threat of VF patients with such episodes were excluded

Melperone had some antiarrhythmic effect on our AMI patients This effect appeared however late after the injection reaching statistical significance

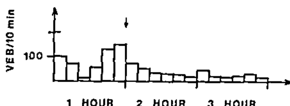


Fig 2 Spontaneous changes in ectopic activity in a patient during the observation hour Arrow indicates mel perone injection

only in the second postinjection hour Only one of ten patients became completely free from warning arrhythmias The results may not be applicable to the very first hours of myocardial infarction be cause most of our patients had infarcts of 4–24 hours duration

The assumption that melperone should act as a type III antiarrhythmic drug is not supported by the present findings It is likely that the antiarrhythmic effect is mediated via the central nervous system and is also separated from the peripheral α blocking effect The injection was immediately followed by a decrease in BP the antiarrhythmic action was coin cident with the peak of the sedative effect and the antiarrhythmic effect was very weak when in farction was absent The absence of antiarrhythmic effect of melperone in the non infarction group might reflect a difference in arrhythmia triggering mechanisms in the infarction and non infarction groups (9) The stable frequency of arrhythmia in the non infarction groups might be due to a lesser susceptibility to a varying degree of stimulation of the autonomic nervous system Melperone produced a decrease in BP within 10 min after injec tion This effect may be beneficial when hyperten sive patients are treated but deleterious in infarct patients who already have a low BP

In conclusion large i v doses of melperone given to a small number of patients with AMI reduced warning arrhythmias The acute BP reduction com bined with the slow onset of antiarrhythmic e limits the use of melperone as an antiarrhyth drug Further studies are justified to see if i m oral melperone in doses well known from psy atric practice will influence arrhythmia and B AMI patients

REFERENCES

1 Arlock P Gullberg B & Olsson S O R Ca electrophysiology of four neuroleptics melpe haloperidol thioridazine and chlorpromazine nyn Schmiedebergs Arch Pharmacol 304 27 197
2 Christensen J A Hernestam S Lassen & Sterner N Pharmacological and toxic studies on γ (4 methylpiperidino) p fluorob phenone (FG 5111)—a new neuroleptic agent Pharmacol Toxicol 23 109 1965
3 Corday E & Lang T W Accuracy of data tion systems for diagnosis and quantification rhythmias Am J Cardiol 35 927 1975
4 Dhurandhar R W MacMillan R L & Brow W G Primary ventricular fibrillation compli acute myocardial infarction Am J Cardiol 2 1971
5 Lie K I Wellens H J Downar E et al vations on patients with ventricular fibrillation plicating acute myocardial infarction Circu 52 7551 1975
6 Lie K I Wellens H J & Durrer D C tics and predictability of primary ventricular lation Eur J Cardiol 1 379 1974
7 Lown B Fakho A M Hood W B et al coronary care unit JAMA 199 188 1967
8 Mogensen L Ventricular tachyarrhythmias nocaine prophylaxis in acute myocardial Acta Med Scand (Suppl) 513 1970
9 Pantridge J F Adgey A A J Geddes J Webb S W The acute coronary attack pp Pitman Medical Belmont 1975
10 Rydén L Waldenström A & Holmberg S reliability of intermittent ECG sampling in arrhyt detection Circulation 52 540 1975
11 Vaughan Williams E M Electrophysiological for a rational approach to antidysrhythmic therapy Advances Drug Res 9 69 1974
12 WHO Ischaemic heart disease registers Repor the fourth working group 1970

Ventricular Arrhythmias During Exercise Testing and 24-Hour ECG Tape Recording in Patients with Ischaemic Heart Disease and in Normal Individuals

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ABSTRACT The occurrence of ventricular arrhythmias (VA) during resting ECG, maximal bicycle exercise testing and 24 hour ECG tape recording (24 ETR) was studied in 24 patients and 24 matched normal persons The patients were on treatment with β-receptor blocking agents or verapamil for ischaemic heart disease (IHD) verified by coronary angiography *The matched persons showed no signs of heart disease* VA did not occur in any of those studied on a 60 second resting ECG During exercise testing one patient and six normal subjects had VA During 24 ETR, VA were found in 16 patients and normal persons The maximum heart rate during exercise and the average heart rate during ETR did not differ significantly between individuals with and without VA in the groups of patients and normal subjects, respectively It is concluded that in IHD patients receiving β-blocking agents or verapamil, 24-ETR is a more reliable indicator of VA than exercise ECG testing In normal individuals the two methods are of similar value

Key words ventricular arrhythmias exercise testing 24-hour ECG tape recording ischaemic heart disease normal individuals

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Ventricular arrhythmias (VA) increase the risk of sudden cardiac death both in persons without symptoms of heart disease (4 7) and patients with known ischaemic heart disease (IHD) (11 13 14)

A resting ECG rarely provides sufficient information about the occurrence of VA in the individual patient (9 16) On the other hand it is difficult at present to determine whether exercise testing or ECG tape recording (ETR) is the most suitable method for the demonstration of VA Some investigators emphasize the value of exercise ECG in patients with IHD (1 5 8) while others consider ETR to be the more suitable of the two methods (3 12 15 17) However several of the authors quoted consider the methods complementary

In order to compare the usefulness of the two methods we studied—by means of resting ECG maximal bicycle ergometer testing and 24-hour ETR (24 ETR)—the pattern of VA in normal subjects and patients with IHD verified by coronary arteriography

STUDY POPULATION AND METHODS

The investigation comprises two age matched groups of men who were studied according to a predetermined plan Their main characteristics are given in Table I

The 24 normal subjects were outpatients and fulfilled the following criteria No symptoms of cardiac disease normal heart stethoscopy normal resting 12 lead ECG normal heart size (X ray of the chest) normal blood pressure no signs of ischaemia on the ECG during maximum exercise testing no drug intake

The 24 IHD patients were fully mobilized during hospitalization All had severe angina pectoris which could not be satisfactorily treated with propranolol 320 mg/day or equipotent doses of other β blocking agents or verapamil A stenosis of 50% or more of at least one of the large coronary arteries had been demonstrated in the preceding 3 months by coronary arteriography in all of the patients Fourteen patients had had acute myocardial infarction (AMI) at least 3 months before the present investigation The antianginous treatment had been gradually discontinued over a period of 3 days prior to the arrhythmia investigation

A resting 12 lead ECG (I–III aVL aVR AVF and V_{1-6}) was recorded for 60 sec with the patient in the supine

Abbreviations VA – ventricular arrhythmias IHD = ischaemic heart disease ETR = ECG tape recording 24 ETR = 24-hour ETR AMI = acute myocardial infarction VE – ventricular extrasystoles

Table I *Clinical characteristics of the two groups*

	Normal group	IHD group
N	24	24
Age (y)		
Mean	53	54
S D	10	7
Previous AMI		14
Therapy prior to study		
Digoxin		3
β blocking agent		11
Verapamil		12
None	24	2

position immediately before start of the exercise testing This was a symptom limiting bicycle ergometer test carried out at a stepwise increasing work load A 6-lead ECG (I–III $V_{1,5}$ and V_6) was continuously registered on a Mingograph 82 (Siemens Elema) from the start until 5 min after discontinuation of the test

After 30 min rest the 24-ETR was commenced using 2 bipolar leads employing a Medilog tape recorder The tape was analysed at 60 times the real speed on a Pathfinder high speed ECG analyser All complicated arrhythmias were printed on paper using the real time The number of QRS complexes and the number of ventricular extrasystoles (VE) were registered during the analysis VA were classified in respect of all three methods of investigation according to Lown and Wolf (10) grade 0 no VE grade 1 isolated unifocal VE grade 2 unifocal VE numbering at least 1 VE/min or 30 VE/hour grade 3 multifocal VE grade 4a paired VE grade 4b three or more consecutive VE grade 5 R-on T phenomenon (RR/QT<1)

Statistical methods

Student's *t* test was employed in the statistical analysis of the results for the comparison of the mean values and the χ^2 test for comparison of the frequencies A significance level of 5% was chosen

RESULTS

Resting ECG

VA did not occur in any of the subjects examined There was no significant difference in the heart rate between the normal and the IHD group (Table II) Neither could any difference in the heart rate be demonstrated between IHD patients with and without previous myocardial infarction or between patients with β blocking or verapamil treatment

Exercise testing

The normal subjects studied had a considerably better working capacity than the patients with IHD (Table II) No difference in the maximum heart was found between IHD patients with and with previous myocardial infarction or patients who received β blocking agents or verapamil The o IHD patient with VA during the exercise testing suffered an AMI three years before and was rec ing no drugs In the normal group 6 persons (2 had VA in connection with the exercise testing all instances a few unifocal VE (Table III) maximum heart rate was not significantly diffe in the normal subjects with and without VA arrhythmias mainly occurred just after the exer The exercise testing was usually performed p m

24 hour ECG tape recording

The average duration of monitoring was equal two groups (Table II) and was carried out cases between 0 and 6 a m In some cases monitoring was terminated before 24 hours due planned coronary arteriography or because the son was unable to return to the hospital at required time The average heart rate did not d significantly between the normal and the group neither during the monitoring as a whole during the period 0–6 a m There was no differ in the heart rate between IHD patients with without AMI neither in respect of the w monitoring period nor the period 0–6 a m Sim ly no difference in the heart rate could be between patients who had been on treatment β blocking drugs or verapamil VA occurred (46%) of the normal subjects and in 16 (67%) of patients with IHD This difference is not statis ly significant During the whole period of m ing two persons in the normal group had mul VE while three patients in the IHD group multifocal VE paired VE or R on T phenom (Table III) During the period 0–6 a m V grade 3–5 were seen in the IHD group only an general the severity of arrhythmias was red during sleep in both groups (Table III) In the I group 10 of 14 patients with previous AMI and 10 without previous AMI had VA The differe not significant No significant difference in the h rate was observed in either group when comp patients with and without VA Similarly the h rate of patients with VA during sleep did not d significantly during this period from that of other patients

II *Resting ECG exercise ECG and 24 ETR in the two groups studied (mean+S D)*

	Normal group	IHD group	p value
esting ECG			
Heart rate (min⁻¹)	66±10	66±10	n s
xercise ECG			
Max heart rate (min⁻¹)	166±22	118+24	<0 001
Total load (kpm)	9 172±5 300	3 330±2 400	<0 001
TR			
Duration (min)	1 279±202	1 190±156	n s
Heart rate (min⁻¹)	78±9	73±11	n s
Heart rate at 0–6 a m (min⁻¹)	63±8	66+10	n s
Mean VE range (hour⁻¹)	0–33	0–40	

ercise testing versus 24 hour ECG tape recording

A occurred more frequently both in the normal bjects and in the IHD patients during ECG tape cording (Table III) but the difference is signifi nt in the IHD group only All patients with VA ring exercise testing also had VA during tape cording The five normal subjects with VA during ep were also among those six who had VA during rcise testing

DISCUSSION

e incidence of VA in a person depends on the istration technique employed and the population died This investigation demonstrates like ers (9 16) that resting ECG is insensitive in the tection of VA It also shows that exercise testing d 24-ETR do not differ significantly in sensitivity regards detection of VA in normal subjects Mul ocal VA however were found only during tape ording The incidences of VA of 25 and 46% re spectively are higher than in the two investigations employing the same methods on normal subjects (2 12) Of 30 normal subjects of roughly the same age as those studied by us 7% had VA during exercise testing against 33% during 24-ETR (12) Only uni focal VE were observed during exercise testing whereas more severe forms of VE were detected in four patients during tape recording In a report comprising 12 patients VA occurred in two persons during exercise testing and in three during tape re cording (2) The methods supplemented each other to a certain extent in another study (12) while the exercise testing in our study did not enhance the information obtained from the 24-ETR alone

We found VA in our IHD patients significantly more frequently during 24-ETR than during exer cise testing The registered incidence of VA of 4% is considerably lower than that of 39–91% detected by exercise testing in other investigations compar ing the two methods (2 6 8 12 15) The low incidence found in our study can be ascribed to the

Table III *Incidence of VA during maximal bicycle ergometer test and 24 ETR in the two study groups*

ximal wn de	Normal group Exercise ECG	Normal group 24-ETR Total period	Normal group 24-ETR At 0–6 a m	IHD group Exercise ECG	IHD group 24-ETR Total period	IHD group 24-ETR At 0–6 a m
[illegible]	18	13	19	23	8	14
[illegible]	2	9	5	1	11	8
[illegible]	4	0	0	0	2	0
[illegible]	0	2	0	0	1	1
[illegible]	0	0	0	0	1	0
[illegible]	0	0	0	0	0	1
[illegible]	0	0	0	0	1	0

massive drug therapy continuing up to the period of monitoring However it is remarkable that such a pronounced antiarrhythmic effect on VA should be observed in patients under treatment both with β blocking agents and verapamil The low incidence of VA might also be accounted for by a low maximum pulse rate during exercise

The incidence of VA of 67% detected by 24 ETR corresponds roughly to that observed in other investigations by 24 hour monitoring as the incidence of arrhythmias is stated to be 78–97% (2 6 12 15) while complicated VA have been found by others in 37–49% (5 12 15) against 8% in the present investigation

The current study shows that VA are detected in normal subjects more frequently by 24 hours of ambulatory ETR than by maximum bicycle ergometer testing and thus that all persons with VA during maximum exercise testing also had VA during tape recording

VE were registered significantly more frequently during 24 ETR than during exercise testing in patients with medicamental intractable angina pectoris under treatment with either a β blocking drug or verapamil Thus it does not appear necessary to supplement 24-ETR with maximum ergometer bicycle testing for the evaluation of VA in patients with this disease

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REFERENCES

1 Åbjorn C Karlsson E & Sonnhag C Ventricular arrhythmias in acute myocardial infarction A comparative study on some tests for ventricular arrhythmias Acta Med Scand 201 119 1977
2 Amsterdam E A Brocchini R Vismara L A & Mason D T Sensitivity of portable monitoring and exercise stress in detection of ventricular arrhythmias in coronary patients Circulation (Suppl) III 213 1974
3 Boudoulas H Dalamangas G Schaal S F Lewis R P & Robinson J L Twenty four hour monitoring and exercise testing in the detection of dysrhythmias In Noninvasive cardiovascular diagnosis University Park Press Baltimore 1978
4 Chiang B N Perlman L V Ostrander L D Epstein F H Relationship of premature syst coronary heart disease and sudden death Tecumseh epidemiologic study Ann Intern 70 1159 1969
5 Crawford M O Rourke R A Ramakrishn Henning H & Ross J Comparative effectiven exercise testing and continuous monitoring for ing arrhythmias in patients with previous myo infarction Circulation 50 301 1974
6 De Backer G Van Durme J P Bogaert Weyne T Comparison of resting ECG e ECG and 24-hour ambulatory monitoring for tion of ventricular dysrhythmias Cardiology 1977
7 Hinkle L E Carver S T & Stevens M frequency of asymptomatic disturbances of rhythm and conduction in middle aged men Cardiol 24 629 1969
8 Kosowsky B D Lown B Whiting R & T Occurrence of ventricular arrhythmias wit cise as compared to monitoring Circulation 1971
9 Lown B Calvert A F Armington R & Ry Monitoring for serious arrhythmias and high sudden death Circulation (Suppl) III 189 197
10 Lown B & Wolf M Approaches to sudden from coronary heart disease Circulation 1971
11 Moss A J DeCamilla J J Davis H P & L Clinical significance of ventricular ectopic b the early posthospital phase of myocardial inf Am J Cardiol 39 635 1977
12 Poblete P F Kennedy H L & Cavalis Detection of ventricular ectopy in patients wit nary heart disease and normal subjects by e testing and ambulatory electrocardiography 74 402 1978
13 Rehnqvist N Lundman T & Sjogren A Pr tic implications of ventricular arrhythmias reg before discharge and one year after acute myo infarction Acta Med Scand 204 203 1978
14 Ruberman W Weinblatt E Goldberg J O F C W & Shapiro S Ventricular premature and mortality after myocardial infarction N E Med 297 750 1977
15 Ryan M Lown B & Horn H Comparis ventricular ectopic activity during 24-hour mon and exercise testing in patients with coronary disease N Engl J Med 292 224 1975
16 Vismara L A Pratt C Price J E Miller R Amsterdam E A & Mason D T Correlation standard electrocardiogram and continuous am tory monitoring in the detection of ventricula rhythmias in coronary patients J Elect graphy 10 299 1977
17 Vorpahl U & Blumchen G Supraventrikulär ventrikulare Extrasystolen bei Patienten in der Postinfarktphase Z Kardiol 67 612 1978

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Episodic Cardiac Arrhythmia and Accident Rate

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ABSTRACT The rate of accidents severe enough to require a roentgen examination was investigated in a series of patients with episodic cardiac arrhythmia of types causing Adams Stokes syndrome The accident rate was doubled compared with controls without known Adams Stokes syndrome but the associated increase in fracture rate was not significant

Key words accident Adams Stokes arrhythmia fracture trauma

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In the past Adams Stokes syndrome was usually considered identical with third degree atrioventricular block Today any arrhythmias—a bradycardia or a tachycardia—capable of causing cerebral symptoms ranging from mild dizziness to full blown syncopal attacks are being included (NYHA Criteria Commission 1973) Recent studies also have revealed that significant episodic cardiac arrhythmias are common among patients with dizziness and syncope (2 5 6 7 8 9 11) Unpredictable falling is a part of Adams Stokes syndrome and it has been shown that 13% of patients treated with pacemakers had been hospitalized because of trauma prior to recognition of the bradycardiac episodes (3) A group of patients treated for postapoplectic dementia who were proven to have occult episodes of severe arrhythmia also in most instances had sustained femoral neck fracture (1)

The aim of this investigation was to estimate the risk of trauma and fracture in a series of patients with occult cardiac arrhythmias with cerebral symptoms in comparison with a control group selected at random

STUDY POPULATION AND METHODS

A consecutive series of 330 patients referred to the Heart Section of the Medical Department due to suspected occult episodic arrhythmia with Adams Stokes syndrome was examined with 24 hour ECG monitoring by means of portable ECG recorders type SRA/HRB 2 (Helcomed Norden/Hellige) The period was extended to more than one day in borderline cases

The tapes were processed by an automatic unit presenting all rhythms faster than 120 or slower than 40 beats/minute by single R–R interval detection as well as every 10th ventricular ectopic beat by configuration criteria as a one lead ECG on a paper strip The ECGs were examined initially by a specialized laboratory technician and finally by one of us (N J A)

Patients with minor arrhythmias such as isolated ectopic beats or sinus arrhythmia with normal rate were omitted from the group The details of the heart examination have been presented elsewhere (1) Significant episodic arrhythmias—i e arrhythmias considered severe enough to cause cerebral symptoms—were present in 173 patients 78 men (mean age 70±14) and 95 women (mean age 72±13) The types and distribution of arrhythmias are listed in Table I

The files of the radiology record room were searched for information about accidents leading to roentgen examinations during the 5 years preceding the diagnosis of arrhythmia Since virtually all emergency roentgen examinations in the city are carried out in the Radiology Department of our hospital an almost complete coverage was attained of trauma episodes sufficiently serious to require a roentgen examination

The following variables were recorded 1) Number of patients who had had one or more roentgen examinations because of trauma 2) Number of accidents which may be suspected of being caused by an episode of dizziness or fainting including falling from standing or sitting position falling downstairs falling off bicycles and similar incidents but excluding injuries obtained as passenger in a

Table I *Diagnoses in 173 cases of significant episodic cardiac arrhythmia*

	N
Supraventricular tachycardia including atrial fibrillation and flutter	29
Sick sinus syndrome—pure bradycardia	32
Sick sinus syndrome—brady tachy	36
Atrioventricular block 2nd degree	5
Atrioventricular block 3rd degree	24
Abundant ventricular ectopics or bigeminy	15
Ventricular tachycardia or coupled ventricular ectopics	32

Table II *Accidents during five years in patients with arrhythmia and in age matched controls*

	Patients			Controls		
	Men	Women	Total	Men	Women	Tot[illegible]
Total no of persons studied	78	95	173	78	95	173
Patients with trauma roentgen	18	22	40	7	13	20
Fall accidents (total no)	31	34	65	9	17	26
Fractures (total no)	8	14	22	4	13	17
Femoral neck fracture	0	3	3	0	1	1

motor-car from beatings and similar accidents in which the patient was an inactive participant 3) Number of fractures diagnosed in conjunction with the accidents under 2 4) Number of femoral neck fractures

To serve as controls 173 individuals were drawn from the population records of the city of Malmö who were identically distributed with regard to sex and age The records of the 173 patients with arrhythmia and the 173 controls were searched in the same way and without knowledge of to which group the individual belonged

RESULTS

The number of patients with one or more traumatic episodes leading to a roentgen examination was significantly increased—doubled—among the arrhythmia cases (Table II) ($0.01>p>0.001$ χ^2 test) Similarly the number of fall accidents and similar accidents was significantly increased—more than doubled—in patients with episodic occult cardiac arrhythmia ($p<0.001$) However there was no significant difference between the two groups in the *number of fractures resulting from all the trauma* episodes Consequently the number of fractures in relation to the number of fall accidents was significantly less among the arrhythmia cases as compared with the controls ($0.01>p>0.001$) The increase in femoral neck fracture rate was not significant

DISCUSSION

A coincidence of femoral neck fracture and episodic arrhythmia previously observed in our department could not be statistically substantiated in this study since the risk of this injury is still fairly low in the age groups *included (4) It must be concluded that* the risk of fall accidents increases during the years of occult arrhythmia episodes preceding the diagnosis In a few instances the accidents may have been the predominant symptom that subsequently led to the consultation and diagnosis thereby i[ntro]ducing unknown but probably insignificant bia[s fac]tor in the selection process Finally the fra[cture] rate remained unchanged in spite of the incr[eased] number of trauma incidents severe enough t[o re]quire a roentgen examination The addition[al re]quirement for low-energy fractures—a re[duced] *bone mass (10)—may be absent in the arrhy[thmia]* cases of this series The interaction of bone fr[agility] and falls caused by Adams Stokes attacks however become important later in life

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REFERENCES

1 *Abdon N J Unrecognized intermittent bra[dycar]dias in patients treated for senile dementia* In [Car]diac pacing the Proceedings of the Vth Intern[ational] Symposium (ed Y Watanabe) Excerpta Med[ica In]ternational Congress Series No 395 Amsterda[m] Oxford 1977

2 — Clinical considerations in the diagnosis of ce[rebral] ischemia caused by episodic cardiac dysrhyt[hmias] In Cerebral manifestations of episodic cardia[c ar]rhythmias (ed H Busse) Excerpta Medica P[rince]ton 1979

3 Abdon N J & Malmcrona R High pacemak[er im]plantation rate following cardiogenic neurol[...] Acta Med Scand 198 455 1975

4 Alffram P A An epidemiologic study of ce[rvical] and trochanteric fractures of the femur in an [urban] population Acta Orthop Scand (Suppl) 65 1964

5 *Goldberg A D Raftery E B & Cashman* [...] M Ambulatory electrocardiographic records [in pa]tients with transient cerebral attacks or p[...] tions Br Med J 4 569 1975

6 Johansson B W Long term ECG in amb[ulatory] practice Eur J Cardiol 5 39 1977

Jonas S Klein B S & Diaman J Importance of Holter monitoring in patients with periodic cerebral symptoms Ann Neurol 1 470 1977
Lipski J Cohen L Espinoza J Motro M Dack S & Donoso E Value of Holter monitoring in assessing cardiac arrhythmias in symptomatic patients Am J Cardiol 37 102 1976
9 McCarthy S & Wollner L Cardiac dysrhythmias Treatable cause of cerebral dysfunction in the elderly Lancet 2 203 1977
10 Nilsson B E & Westlin N E Bone mineral content and fragility fractures Clin Orthop 125 196 1977
11 Walter P F Reid S D & Wenger N K Transient cerebral ischemia due to arrhythmia Ann Intern Med 72 471 1970

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Episodic Cardiac Arrhythmia and Femoral Neck Fracture

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ABSTRACT Fifty eight consecutive patients admitted to hospital for fracture of the upper end of the femur were examined by continuous ECG monitoring 22–24 hours More than one third of the patients had occult previously unknown episodic arrhythmias severe enough to cause dizzy spells and syncope These patients had more often a history of dizziness and syncope and could less frequently than patients without serious arrhythmias return to their homes at the time of discharge despite uncomplicated fracture treatment

Key words arrhythmia ECG fracture femoral neck

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Episodic cardiac arrhythmias may cause dizziness and fainting In patients with such symptoms serious episodic arrhythmias have been found by continuous ECG monitoring in incidences ranging from 20 to 74% (2 5 6 7 8 11) Increased risk of trauma is common in patients with episodic arrhythmia causing dizziness and syncope In a series of patients with Adams Stokes syndrome treated with pacing no less than 13% had been admitted to hospital because of trauma prior to pacemaker implantation (3) This liability disappeared during pacemaker treatment Transient cardiac arrhythmia is an elusive condition which may not be recognized for a long time or ever

Femoral neck fracture—fracture of the upper end of the femur—is related to aging (4) and impaired quality of the bone and is regarded as one of the typical symptoms of bone fragility (9) However it is generally agreed that a trauma in most instances is needed to cause a fracture even if the trauma in itself would not cause injury to a subject with an intact bone quality

The two conditions—fracture of the neck of the femur and occult cardiac arrhythmia—are both common in an aging population The purpose of the present investigation was to study the possible role of occult arrhythmias in patients with femoral neck fracture

PATIENTS AND METHODS

Included in the study were 58 consecutive patients aged 51–91 (77±11) 12 men (aged 73+11) and 46 women (aged 78±11) admitted to the Orthopedic Department Twenty six of the fractures were trochanteric and 32 cervical None of the patients had local bone destructions or other findings indicating a pathological fracture one woman had a somewhat dubious impacted cervical fracture The fractures were eventually treated with reduction and osteosynthesis but were in all managed in traction for at least 24 hours of preoperative preparations On admission a detailed cardiac and neurological history was recorded in each case A radiogram of the heart and lungs was performed in all patients in connection with the diagnosis of fracture

Preoperatively a continuous ECG monitoring covering 22–24 hours was performed using portable ECG tape recorders type SRA/HRB 2 (Helcomed Norden/Hellige) There was no change in the cardiac medication until the ECG recording was completed except for a few patients who received diuretics due to congestive heart failure The ECG tapes were stored and analyzed after discharge using an automatic screening unit Rhythms faster than 120 or slower than 40 beats/minute detected by single beat to-beat interval triggered the screening unit to present the event as a written one-channel ECG on a paper strip In addition every 10th premature ventricular contraction (PVC) detected by QRS configuration criteria was presented The further diagnostic procedure included a screening by specially trained laboratory technicians and finally by one of us (N J A)

All signs of arrhythmia were recorded Minor arrhythmias of types normally occurring in healthy subjects have been referred to as insignificant Major arrhythmias with an inherent capacity of causing cerebral symptoms were considered significant Such significant episodic arrhythmias were Abundant PVCs—i e every 5th beat or more frequently—coupled PVCs and ventricular tachycardias defined as three consecutive PVCs at a rate of at least 100 beats/min atrial tachycardias including fibrillation and flutter providing a ventricular rate of 120 beats/min or more and a duration of more than 8 sec atrioventricular

Abbreviations PVC=premature ventricular contraction PAC = premature atrial contraction SSS – sick sinus syndrome

blocks of grades 2 or 3 and finally the sick sinus syndrome (SSS) fulfilling one or more of the following criteria 1) Sinus bradyarrhythmias of 50 beats/min or less 2) Regular sinus bradycardia of 45 beats/min or less when awake 3) Sinoatrial block with more than one P wave missing 4) Sinus arrests of 1 5 sec or more

In addition to the monitored ECG serial 12 lead routine ECGs were recorded and serial S GOT and S-GPT determinations were made for three consecutive days after admission This procedure revealed no case of definite or suspected acute cardiac disorder

In addition to the detailed questionnaire used on admission the record room of the Medical Department was searched for information on earlier complaints of dizzy spells and syncope as well as cardiac symptoms in the fracture patients The record room of the Roentgen Department was also searched for information on trauma episodes for the last five years preceding the femoral neck fracture The City of Malmo is served by one single hospital—the General Hospital—and the emergency room of the Medical Department is the only unit available for emergency consultations regarding neurological or cardiac symptoms Thus it is assumed that the overwhelming majority of such patients are registered in the record room of the department Practically all trauma roentgen is also carried out in the General Hospital

The fracture patients were compared with 103 individuals randomly selected from the population at risk 53 men and 50 women with an average age of 71 years (range 47–92) who had been studied with regard to arrhythmias using the very same method of 22 hour continuous ECG monitoring Out of these individuals 26 had complaints of dizzy spells whereas 77 denied all forms of dizziness or syncope

RESULTS

Patients with insignificant arrhythmias only

In 35 patients aged 75±11 no or only insignificant episodic arrhythmias were detected One had chronic atrial fibrillation with an appropriate ventricular rate 34 were in sinus rhythm Fourteen patients had infrequent (i e less than every 10th beat) premature atrial contractions (PACs) and 8 had abundant or moderately frequent PACs (i e at least one PAC in 5 and 6–10 beats respectively) Two patients had short bursts of atrial tachycardias lasting for 8 sec or less Eighteen patients had infrequent or moderately frequent PVCs

Patients with significant episodic arrhythmias

In 23 patients aged 79±10 significant episodic arrhythmias were detected (Table I) Six patients had episodes of atrial tachycardias including fibrillation lasting longer than 8 sec with ventricular rates of 120 beats/min or more Nine patients had abundant

Table I *Episodic arrhythmias in 77 asym[illegible] controls and 58 patients with fracture of the [illegible] end of the femur*

	Asymptomatic controls		Fra[illegible] cases
	N	%	N
SSS	3	4	2
Attacks of rapid supraventricular rhythms	2	3	6
High-frequency PVCs ventricular bigeminy	4	5	9
Ventricular tachycardia			3
Atrioventricular block grade 2 or 3			3
	9	12	23

$p<0\ 001$ (χ^2 test)

PVCs or ventricular bigeminy and three had [illegible] tricular tachycardias Episodes of sinus bradyc[illegible] fulfilling the criteria used for SSS were pres[illegible] two patients and transient atrioventricular blo[illegible] grade 2 or 3 was present in three patients

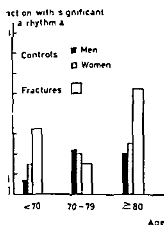
Mortality and discharge from hospital

Five of the 23 patients with significant arrhy[illegible] and four of 35 without died during hospitaliz[illegible] This doubled mortality was however not s[illegible] tically significant Despite uncomplicated fra[illegible] healing only 4 of the 18 surviving patients [illegible] significant arrhythmias had a general physical [illegible] dition permitting return to their homes after [illegible] charge whereas 15 of the 31 survivors wi[illegible] significant arrhythmias could return to their h[illegible] without permanent or transient need for in[illegible] tional care Again the difference was not sign[illegible] There were no signs of acute cardiac disease [illegible] of the 58 patients—the subsequent departure [illegible] the cases was in most instances due to pulmo[illegible] embolism

The ratio cervical/trochanteric fractures was [illegible] 16 in the group without and 13/10 in the grou[illegible] significant arrhythmias

Previous dizziness and significant arrhythm[illegible]

Fifteen out of the 23 patients with and 12 out of 35 patients without significant episodic arrhy[illegible] had visited the Department of Medicine beca[illegible] dizziness and/or syncope or had reported th[illegible] of symptoms on admission for fracture ($p<0$[illegible]



— *1* Incidence of significant arrhythmia in fracture es compared with all normals symptomatic as well asymptomatic

~e admission chest X ray showed cardiac en rgement in 5/23 of the arrhythmic cases and in 35 of those without significant arrhythmia There s no significant difference in this aspect How r resting ECG showed definite previous ocardial infarction ischemic T wave inversions arrhythmia in 7/23 arrhythmic patients and 1/35 patients without significant arrhythmia is difference is statistically significant (0 01> 0 001)

There was no difference in the frequencies of her trauma episodes between fracture patients h and without significant arrhythmia

mparison with normals

nificant arrhythmia was approximately three es as common in femoral neck fracture cases as the asymptomatic controls (Table I) The ar thmias in the fracture group were also more ious and long lasting than in the asymptomatic rmals However it must be taken into account t the age and sex distribution of the two groups s different The 26 symptomatic normals who nonstrated significant arrhythmia in 12 cases ild also be included in the comparison The age l sex incidence of symptomatic arrhythmia is sented in Fig 1 including all 103 normals The idence shows a tendency to increase with in asing age but does not differ significantly be een the sexes When comparing the femoral neck cture cases with the normals taking the age into ount there is still a significant difference in the prevalence of arrhythmia among the youngest and the oldest in the two groups

DISCUSSION

As pointed out above serious episodic arrhythmias have been demonstrated in a high incidence in patients with dizziness and syncope However only few asymptomatic individuals even of ad vanced age have serious episodic arrhythmias (2 10) The findings of the present study indicate a significant increase in serious episodic arrhythmias a possible contributory cause of fracture This view is supported by the findings in 32 patients 20 of whom had episodic arrhythmias treated for post apoplectic dementia in a psycho geriatric hospital in the City of Malmo Not less than 11 had also sustained a fracture of the upper end of the femur (1) Among 23 demented patients in the same hos pital but without episodic arrhythmia only 2 had had femoral neck fracture

Fracture of the neck of the femur is a stressful condition possibly capable of triggering arrhyth mia Arrhythmia then would be a result rather than a cause of the trauma However patients with sig nificant arrhythmias had more often a history of dizziness than those without Furthermore since patients with significant arrhythmia had a markedly increased need of institutional care following the fracture episode it might be argued that even if the trauma has triggered off the arrhythmia in some cases this tendency might nevertheless be inherent with the patient and regardlessly resulting in a poor prognosis

The mortality among our 58 fracture patients was about 15% which is in agreement with the mortality figure in a previous study of the same population (4) Although the difference between the two groups is not significant both the mortality and the ability of the patient to sustain without institutional care after discharge from hospital indicate a worse post fracture course for femoral neck fracture patients with serious arrhythmia even if the age factor must be taken into consideration The most serious pros pect for these patients is probably the increased risk of continuing impairment of the cerebral function The method of continuous ECG monitoring has proven its value in the diagnosis of occult episodic cardiac arrhythmia and will probably be a routine diagnostic tool in the future Patients with fracture of the upper end of the femur appear to be a worth while target for such diagnostic efforts

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REFERENCES

1 Abdon N J Unrecognized intermittent bradycardias in patients treated for senile dementia In Cardiac pacing the Proceedings of the Vth International Symposium (ed Y Watanabe) Excerpta Medica International Congress Series no 395 Amsterdam and Oxford 1977
2 — Clinical considerations in the diagnosis of cerebral ischemia caused by episodic cardiac dysrhythmias In Clinical manifestations of episodic cardiac dysrhythmias Excerpta Medica Amsterdam 1979
3 Abdon N J & Malmcrona R High pacemaker implantation rate following cardiogenic neurology Acta Med Scand 198 455 1975
4 Alffram P A An epidemiologic study of cervical and trochanteric fractures of the femur in an urb population Acta Orthop Scand (Suppl) 65 196
5 Goldberg A D Raftery E B & Cashman P M Ambulatory electro-cardiographic records patients with transient cerebral attacks or pitations Br Med J 4 569 1975
6 Johansson B W Long term ECG in ambu practice Eur J Cardiol 5 39 1977
7 Jonas S Klein I B S & Diamant J Impo of Holter monitoring in patients with periodic ce symptoms Ann Neurol 1 470 1977
8 McCarthy S T & Wollner L Cardiac rhythmias Treatable cause of cerebral dysfunc the elderly Lancet 2 203 1977
9 Nilsson B E & Westlin N E Bone mineral c and fragility fractures Clin Orthop 125 196 19
10 Raftery E B & Cashman P M M Lon recording of the electrocardiogram in a population Postgrad Med J (Suppl) 7 32 1976
11 Walter P F Reid S D & Wenger N K Tr cerebral ischemia due to arrhythmia Ann Inte 72 471 1970

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Atrioventricular and Intraventricular Conduction in Familial Amyloidosis with Polyneuropathy

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ABSTRACT Atrioventricular and/or intraven cular conduction disturbances were found in 48 (?%) out of 71 patients with familial amyloidosis with polyneuropathy Low voltage often described in various forms of heart amyloidosis was seen in one patient only Myocardial infarction patterns also of reported in heart amyloidosis were not present in our patients The prevalence of conduction disturbances increased with the duration of the disease In out of 47 patients from whom more than one ECG recording was available a progression of conduction disturbances could be seen Ten patients developed high degree conduction disturbances and required permanent pacemaker treatment

Key words amyloidosis ECG
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During the last few decades several heredofamilial syndromes have been recognized which all have in common a systemic accumulation of amyloid and polyneuropathy (9) One type of familial amyloidosis with polyneuropathy (FAP) characterized by sensorimotor disturbances affecting the lower extremities more severely than the upper and widespread autonomic dysfunction was originally described in Portugese patients (2) Kindreds with the same disease have now also been reported from other countries e g Japan (3) Sweden (1) and England (16)

In many of the various forms of primary amyloidosis described heart affection is of major importance and these patients often succumb to heart failure (4 7) The ECG findings most suggestive of cardiac amyloidosis are generally said to be low voltage myocardial infarction patterns and to a lesser degree rhythm and conduction disturbances (12) In previous reports on FAP of the type originally reported from Portugal cardiac amyloid deposits were common autopsy findings (6 10 11 16) Angina pectoris and heart failure were uncommon among these patients but ECG signs of heart dysfunction were common (1 6 15 16)

The purpose of this report is to assess the occurrence of ECG abnormalities especially QRS changes and conduction disturbances in Swedish patients with FAP Special attention is paid to the natural history of conduction disturbances in this disease

PATIENTS

The study concerns 71 patients 46 men and 25 women 66 of whom were admitted to the Department of Internal Medicine University Hospital Umeå and five to other hospitals in the Umeå region The records of the latter five patients were available for our study All patients had symptoms and signs of polyneuropathy and amyloidosis was confirmed in all during their life time by histological examination of biopsy material No chronic inflammatory disease myelomatosis or tumors were found in any of the patients This study includes all known patients with verified FAP in the Umeå region with at least one available ECG recorded after the onset of symptoms

The first symptoms had appeared at the age of 25-81 years (mean 55) Thirty four patients are dead They survived 4-21 years (mean 10) after the onset of symptoms Thirty seven patients are still alive and have been observed for 2-24 years (mean 9) after the onset of symptoms ECGs were recorded at varying intervals For 24 patients only one recording was available two or more for 47

Digitalis had not been given to any of the patients with a high-degree conduction disturbance Other drugs which can influence AV conduction—such as β blockers quinidine or procainamide—were not given to any of our patients

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Abbreviations FAP=familial amyloidosis with polyneuropathy AF atrial fibrillation AV=atrioventricular IV=intraventricular LAH=left anterior hemiblock LPH=left posterior hemiblock LBBB left bundle branch block RBBB=right bundle branch block

Table I *Atrioventricular and intraventricular conduction defects in 71 patients with familial amyloidosis with polyneuropathy*

Patients with LAH+RBBB are also included in the LAH and RBBB groups

	N	%
AV block	27	38
I	19	27
II	1	1
III	7	10
IV conduction defects	29	41
LAH	19	27
LBBB	7	10
RBBB	9	13
LAH+RBBB	6	9
AV block+IV conduction defect	9	13

METHODS

Biopsies for histological examinations were taken from skin rectal mucosa or the sural nerve and the specimens were examined after Congo red staining in polarized light (13) A 12 lead ECG (I II III aVR aVL aVF and six chest leads) with the conventional amplificaton (1 mV = 10 mm) and at a paper speed of 50 mm/sec was recorded using a direct writing ECG apparatus (Siemens Elema Ltd Solna Sweden) The ECG evaluation included a classification of the ECG abnormalities according to the Minnesota code (14) The criteria of Castellanos and Lemberg (5) were used for left anterior and left posterior hemiblocks (LAH and LPH)

RESULTS

Abnormal ECGs were found in 62 (87%) of 71 patients In nine patients the ECGs were normal 1–12 years after the onset of symptoms Atrioventricular (AV) and/or intraventricular (IV) conduction defects occurred in 48 (67%) of the patients The various conduction defects seen at the last investigation of each patient are given in Table I Atrial fibrillation (AF) with or without IV conduction defects was present in 10 (14%) patients Low voltage was found in one patient No postinfarction changes were seen in this patient series Nonspecific ECG changes such as occasional ventricular or supraventricular premature beats or repolarization abnormalities were not analyzed in detail in this study

The prevalence of conduction disturbances increased with the duration of the disease and only three of the patients examined more than 10 years after the onset of symptoms had normal impulse conduction Table II shows the prevalence duction disturbances from ECGs recor various intervals

Among 28 of the 47 patients from whoi than one ECG recording was available du period of observation a progression could served from normal impulse conduction form of AV or IV conduction disturbance o more low-degree to a more advanced co disturbance Reversal of conduction distu was not seen Ten of our patients requi manent pacemakers seven because of A III one because of AF with slow ventric left bundle branch block (LBBB) and fain sodes one because of AF right bundle block (RBBB) LAH and fainting episodes because of AV block I LBBB and s Adams Stokes attacks

Two case hisories illustrate the pr nature of the conduction disturbances

Case 1

A female born in 1904 was admitted to the h times for periods of varying length from 1962 to in 1971 The family history revealed nothing of the time of the first admission FAP was diagnos two of her relatives From 1958 onwards she h enced increasing symptoms with paresthesias disturbances and muscular weakness and atr affecting the legs but extending a few years la upper extremities From 1960 onwards she suff gastrointestinal disturbances with bouts of d nating with periods of constipation

The diagnosis of FAP was established in 1 amyloid deposits were found in biopsy materia rectal mucosa An ECG recorded on initial Dec 1962 revealed AV block I with P–Q time LAH The heart volume was normal The p experienced periods with palpitations but had heart symptoms Fainting episodes occurred i tumn of 1967 and AV block I with P–Q tim RBBB and LAH were found in Oct 1967 In J complete AV block with ventricular rate of 36 registered A permanent right ventricular tra pacemaker was then inserted From that time o ther syncope episodes occurred and there were n cardiac incompensation

The patient died suddenly from a cerebral thro Jan 1971 At autopsy the heart was found to be (weight 620 g) The coronary arteries showed *atherosclerosis Abundant amyloid deposits were* the myocardium Amyloid deposits were also specimens from peripheral nerves intestinal mu nal medulla and the thyroid

Case 2

A man born in 1905 into a family in which seve bers have FAP He was in good health until 1961

ɔle II *Atr o entr c lar a d tra entr c lar c t on defects and atr al f br llat ı p t ents fa n l al n lo dos s tl p l e r p tl alenc t d fferent ter als after tl e ı nset of p on s pat e ts exan d n tl at nt r l*

en mo e than one ECG was reco ded n an nter f nd ngs at the last one a e g en F nd ngs at the reco d ng prior to pacemaker mplantat on are given pa ents t eated w h pacemake s Nonspec f c ECG nges nclude ven ncular and supraventricular ectop c ts and repolariza on abnormal t es The pat en s w th H RBBB are also ncluded n the LAH and RBBB ups

	In erval after onset of symp oms (y)					
· of pa s m ned	0–4 50		5 9 35		≥10 16	
	N	%	N	%	N	%
mal ECG o non c f c ECG changes	25	50	9	26	3	19
block	11	2	16	46	7	44
	8	16	13	37	4	5
	1	2	0	0	1	6
I	2	4	3	9	2	13
onduc on defects	15	30	16	46	11	69
AH	12	4	11	31	4	25
BBB	1	2	3	9	4	5
3BB	4	8	5	14	5	31
AH RBBB	2	4	3	9	2	13
block IV duc on defec	3	6	9	26	3	19
	6	12	3	9	3	19

n hen on suffe ed from p ogress ve polyneuropathy mpo ence F om 1970 onwards he also had troub me ep sodes of d arrhea The d agnos s was estab ed n 1966 when amylo d depos ts were found n b opsy enal from the rec al mucosa Progress ve muscula tage and we ght loss ensued but no h story cons s ent card ac failure or angina pectoris and the pat ent e experienced any fa nt ng ep sodes In Sept 1963 a mal ECG was recorded In Oct 1966 the P–Q t me still normal but RBBB was found At the same me s X ray showed normal heart volume and con ration In March 1970 the last ECG recorded showed block I w h P–Q t me 32 cs RBBB and LAH The ent d ed suddenly n Feb 1975 No au opsy was formed

DISCUSSION

h s retrospect ve survey of the ECG f nd ngs in ed sh pat ents w th FAP we could not recognize pattern often sa d to be more or less typ cal of mary amylo dos s w th heart affect on that is a h gh prevalence of lo v voltage and myocard al in farct on patterns (4 12)

The h gh prevalence of AV and IV conduct on defects n our pat ents is cons stent with the f nd ngs in a recent report on ECG changes in 190 Portugese pat ents with FAP (8) One notable d f ference between our and the Portugese pat ents is the lack of more high-degree conduct on d sturb ances such as AV block III and b fascicular block among the Portugese pat ents Ho ever the age d fference bet een the Swed sh and Portugese pat ents makes it d ff cult to compare the two pat ent groups d rectly as does the lack of data n the Portugese report concern ng the duration of the d sease

In many of our pat ents for whom repeated ECG record ngs were available we could observe a pro gress on in the conduction defects The case reports illustrate the stepw se nterrupt on of impulse prop-agat on wh ch can be seen in these pat ents Th s progressive conduct on system d sorder leads fre quently to l fe threaten ng d sturbances and 10 of our 71 pat ents requ red pacemaker treatment

Noth ng s known about the pathophysiological background of the conduct on d sturbances n th s d sease Amylo d inf ltrat ons w th spec al aff n ty to the conduct on system m ght be one cause How ever if th s s indeed the cause it is somewhat strange that there should be no LPH Involvement of the autonom c nerves of the heart m ght be another contributory factor lead ng to the conduc tion d sturbances As yet there has been no h s topatholog cal exam nation of the conduct on sys tem in pat ents w th FAP but such a study has now been n t ated in our hosp tal

REFERENCES

1 Andersson R Hered tary amylo dos s w th polyneuropathy Acta Med Scand 188 85 1970
2 Andrade C A pecul ar form of peripheral neuro pathy Fam l ar atyp cal generalized amylo dos s w th spec al nvolvement of the peripheral nerves Bra n 75 408 1952
3 Araki S Mawatari S Ohta M Nakaj ma A & Kuro wa Y Polyneuri c amylo dos s n a Japanese family Arch Neurol 18 593 1968
4 Buja L M Kho N B & Roberts W C Cl n cally s gn f can card ac amylo dos s Am J Card ol 26 394 1970
5 Caste lanos A J & Lembe g L D agnos s of solated and comb ned block in the bundle branches

and the divisions of the left branch Circulation 43 971 1971
6 Coelho E & Pimentel J C Cardiac involvement in a peculiar form of paramyloidosis Am J Cardiol 8 624 1961
7 Fredriksen T Gøtzsche H Harboe N Kiær W & Mellemgaard K Familial primary amyloidosis with severe amyloid heart disease Am J Med 33 328 1962
8 Freitas A F & Barbedo A Conduction disturbances in 190 patients with familial amyloidotic poly neuropathy (Andrade s type) Adv Cardiol 21 206 1978
9 Glenner G G Ignaczak T F & Page D L The inherited systemic amyloidosis and localized amyloid depositions In Metabolic basis of inherited diseases (ed J B Stanbury J B Wyngaarden and D S Fredrickson) pp 1308-1339 McGraw Hill New York 1978
10 Hofer P Å & Andersson R Postmortem fi[illegible] in primary familial amyloidosis with polyneur[illegible] Acta Pathol Microbiol Scand 83 309 1975
11 Horta J S Filipe I & Duarte S Portugese [illegible] neuritic familial type of amyloidosis Pathol Mic[illegible] 27 809 1964
12 Marriott H J L In Practical electrocardiogr[illegible] p 308 Williams and Wilkins Baltimore 1975
13 Missmahl H P & Hartvik M Polarisationsopt[illegible] Untersuchungen an der Amyloidsubstanz Vir[illegible] Arch Pathol Anat 324 489 1953
14 Rose G A & Blackburn H In Cardiova[illegible] survey methods pp 137-141 WHO Geneva 19[illegible]
15 Sawayama T Kurihara T & Araki S Nonin[illegible] cardiovascular findings in familial amyloid neuropathy Br Heart J 40 1288 1978
16 Zalin A Darby A Vaughan S & Raftery E[illegible] Primary neuropathic amyloidosis in three brothe[illegible] Med J 1 65 1974

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A Study of Stroke Patients Treated in a Non Intensive Stroke Unit or in General Medical Wards

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TRACT To study the representativity and out of patients admitted to a stroke unit (SU) 269) a comparison was made with all stroke pa s treated in general medical wards (GMW) 225) in the same hospital during two years There no d fference between the pat ent groups regard sex age previous card ovascular diseases or olog cal deficit on admission As expected more nost c examinat ons were performed in the SU in the GMW where a diagnosis of ill defined ke was very frequent A higher frequency of lum puncture with CSF spectrophotometry would increased considerably the number of specific noses in the GMW Acute and particularly sec ary prophylactic treatment was more often given he SU There was no difference between the pa t groups regarding mortality or length of hospital

Wo ds acu e cereb ovascula d sease prognos s

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re have been several arguments for and aga nst ke ntensive care un ts or neurovascular un ts nly due to lack of effect ve specif c med cal tment in the acute phase of cerebral infarct on work n such un ts has concentrated on supervi i of card ovascular funct ons (7) and early and ve treatment by e g phys otherap sts (15) wever only a few authors have reported a de sed mortal ty or morb dity n these un ts (13 Most invest gators have not been able to show h pos t ve effects but have stressed the impor e of the Stroke Un t (SU) as a basis for research educat on (7 8 11 14 16 17 20) he reason for establ sh ng a non ntens ve SU at the Medical Department of Seraf merlasarettet in 1976 was to create a basis for scient f c stud es Our a m was to evaluate d agnost c procedures n order to form an investigat on program for non selected pat ents of all ages with acute cerebrovascular d s ease (CVD) We also wanted to study d fferent therapeutic measures during the acute phase of stroke as well as the effects of long term secondary prophylactic treatment As background to these stud es t was considered of value to compare stroke patients adm tted to the SU with stroke pat ents treated n the general med cal wards (GMW) during the same period

The a ms of the present study were to answer the following quest ons 1) Were the stroke patients adm tted to the SU representat ve of all pat ents with stroke treated in our hosp tal during the study period? 2) Did the diagnost c invest gation program appl ed in the SU result in a d fferent distribut on of the d agnoses of CVD and more aggressive treat ment there than in the other wards? 3) D d the outcome during the hospital period d ffer between the two pat ent groups?

PATIENTS AND METHODS

Seraf merlasarettet serves a populat on of about 1 0 000 nhab tants n Greater Stockholm and about 300 stroke pat ents are adm tted annually The Med cal Department has 185 beds n e ght med cal wards Except for the Coronary Care Un t there is no bas c d fference n pat ent care between the wards

The study period comprised two years Dec 1976–Nov 1978 In ally there were only f ve beds for women n the

Abbre at ons CVD = cerebrovascular d sease SU stroke un t GMW general med cal wards TIA tran s ent schaem c a tacks CSF cerebrosp nal flu d ICD internat onal class f cat on of d seases

Table I *Age and sex distribut on and previous diseases registered in the ad nission form of patients treated in the SU or GMW*

	SU (n 769)	GMW (n 725)
Men		
%	45	37
Mean age (y)	71	7?
Women		
%	55	63
Mean age (y)	75	76
Previous diseases (%)		
Stroke	19	17
TIA	11	9
Hypertension	4?	39
Heart failure	31	?6
Atrial fibrillation	18	?0
Angina pectoris	14	11
Myocardial infarction	11	1?
Diabetes mellitus	10	1?
None of these	19	?3

All differences were statistically non significant

SU In April 1977 five beds for men were added For th s reason only women treated n the GMW were cons dered for comparison during the first four month period After that and during the remaining study period all men and women w th a d agnos s of acute CVD were included

All pat ents with suspected acute CVD fulfilling the following admission criteria in the Casualty Department were admitted either to the SU if a bed was available or to a GMW 1) Transient ischaemic attacks (TIA) Patients w th one or more episodes of focal neurological deficit with a duration of less than ?4 hours w th n the last month Attacks of vertigo or syncope w thout focal neurological deficit were not included ?) Progressive and manifest stroke Patients with acute onset of focal neurological deficit during the previous week and w thout preceding trauma to the head

In the Casualty Department a special record (?) based on a neurological score system was filled in by the examining doctor for all such patients A high score (→100) meant a better prognosis for the hospital period (10) The history of present and past illnesses was also noted in these records One of the authors (K M) checked the admission register at the Casualty Department every day to control all stroke patients admitted to the hospital If necessary the patient was re-examined in the ward and the hospital record was consulted for missing data

The Stroke Unit

The resources for general patient care in the SU did not differ from those in the GMW There were no facilities for intensive care in the unit A preplanned investigation program including lumbar puncture with spectrophotometry skull X ray with echoencephalography and brain scan was adhered to Strict criteria for d[...] and treatment were followed as described e[...] (3 4)

All categories of personnel have been speciall[...] cated at weekly conferences and an early act[...] to mobilization and rehabilitation planning has bee[...] sed A close co-operation between all categories [...] sonnel has also been developed

Minimum diagnostic requirements

(A) Fulfillment of admission criteria *(B)* 1) C[...] haemorrhage according to international classifica[...] diseases (ICD) (?4) (ICD 431) Macroscopica[...] rhagic cerebrospinal fluid (CSF) or bleeding pa[...] spectrophotometry 2) Cerebral thrombosis a[...] cerebral arterial occlusion (ICD 43? 433) Absen[...] bleeding pattern at spectrophotometry of the C[...] Cerebral embolism (ICD 434) Sudden onset of sy[...] in patients with atrial fibrillation valvular disease[...] nificant atherosclerotic changes in the relevant artery Findings at spectrophotometry in accordan[...] an ischaemic les on 4) TIA (ICD 435) Focal ne[...] cal deficit w th a duration of less than ?4 hours [...] but ill-defined CVD (ICD 436) Patients with CVD not fulfill the minimum requirements for a specific[...] nosis

General medical wards

The principles of investigation and management o[...] patients differed between medical wards according [...] routines of the consultant physician A discharg[...] mary is written for all patients at the time of d[...] The hospital records and summaries of all patients [...] diagnosis of acute CVD fulfilling the admission [...] were studied with regard to present and past ill[...] physical examination results of laboratory and X-[...] amination treatment and progress during hospita[...] diagnosis and discharge If our neurologist ha[...] consulted his report was studied and so were all [...] reports For the purpose of comparing the GMW p[...] with those treated in the SU the final diagnoses in [...] charge summaries were reconsidered and when [...] sary changed according to the diagnostic criteria [...] above

Statistics

The χ^2 test was used for testing the significance of d[...] ences of proportions Two-sample t test was used [...] differences between means Degrees of significance [...] tested at 5 1 and 0 1% levels

RESULTS

General characteristics of the patients (Table I)

During the study period a final diagnosis of C[...] was established at discharge in ?69 patients [...] age 73 years range 50-9?) in the SU and in [...]

ple II *D agnoses n the d scl arge s n mar es of pat ents treated in tl e GMW and tl e f nal d agnoses co d ng to tl e d agnost c cr ter of tl e SU*

agnos s n the scharge summaries	F nal d agnoses Cerebral haemorrhage	Cerebral th ombos s	Cerebral embol sm	TIA	Acute ll def ned CVD	Total
:rebral haemorrhage	16	3			4	23
:rebral th ombos		17	4		2	23
:rebral embol sm		4	17		8	29
A		1		29	1	31
:u e ill-def ned CVD	7	32	16	2	62	119
ital	23	57	37	31	77	225

nts (mean age 74 years range 41 100) n the MW Somewhat more men than women were ad itted to the SU but the d fference was not statisti lly s gnif cant The mean neurolog cal score on m ss on was 61 in both groups The prevalence of portant prev ous d seases d d not d ffer between e two groups

agnost c n est gat ons

umbar puncture w th CSF spectrophotometry was rformed n 94% of cases in the SU as compared r 50% in the GMW ($p<0\ 001$) Skull X ray and hoencephalography were performed in 94% and a n scan n 83% n the SU compared to 35% and % respectively in the GMW ($p<0\ 001$) Arch g ography was performed as often in the GMW 3%) as in the SU (11%) Autops es were per rmed in 45 (92%) of 49 deceased n the SU and in (73%) of 45 n the GMW

str b t on of d agnoses

ter recons derat on the d agnoses were changed 84 pat ents (37%) treated in the GMW (Table II) e f nal d stribution of d agnoses is presented in ble III S nce less nvest gat ons were performed the GMW the ll-def ned group was considerably ger there than n the SU Cerebral thrombosis d cerebral embol sm were sign f cantly more mmon d agnoses in the SU wh le TIA was more quent in the GMW

te t eatment and secondary propl lax s

ve of the SU pat ents w th repeated TIA or pro- ss ve stroke rece ved heparin compared to two t ents with TIA and one with progressive stroke the GMW Of the SU pat ents w th cerebral nfarc n 46 were included n a double bl nd study w th continuous i v theophyll ne (5) Of the pat ents with non haemorrhagic d agnoses and d scharged al ve 72% in the SU and 35% in the GMW received acetylsal cyl c ac d and/or d pyridamol as prophylact c treatment Ant coagulant treatment (warfarin) was inst tuted in 13% of the SU pat ents and in 12% of the GMW pat ents Carot d endar terectom es were performed in 8 patients n the SU and 2 in the GMW

Sl ort ter o tco e

There was no d fference n hosp tal mortal ty or length of hosp tal stay (21 days in the SU and 20 days n the GMW) between the two pat ent groups The proport ons of pat ents sent home and to re hab l tation hosp tals were also s m lar (Table IV)

DISCUSSION

The criter a for admiss on to the SU have prev ous ly been shown to be val d (sens t vity 86% spec f c ty 99%) for dent f cat on of pat ents w th suspected CVD adm tted to hosp tal (1) The pa

Table III *Percentage d str b t on of f nal d ag noses and mortal t (n parentheses) n tl e SU and GMW*

	SU (n 269	GMW (n 25)	p
Cerebral haemorrhage	8 (50)	10 (61)	NS
Ce ebral thrombos s	58 (12)	25 (10)	<0 001
Cerebral embol sm	24 (27)	16 (2)	<0 05
TIA	8 (0	14 (0	<0 05
Acute ll-def ned CVD	2 (40	34 (9	<0 001

p values nd ca e d ffe ences in d agnos s differences n mortal ty we e not s gn f cant

Table IV. *Mortality and discharge after the hospital period (%)*

	SU (n=[illegible])	GMW (n=225)
Hospital mortality	18	16
Discharged		
Home	[illegible]	[illegible]8
To rehabilitation homes	36	35
To other clinics	[illegible]	1

All differences were statistically insignificant.

tients with suspected stroke who came to the Casualty Department were meant to be admitted to the SU or to the GMW without any selection. Nevertheless, some selection may occur in spite of such an intention, e.g. more seriously ill as well as younger patients are preferably transferred to the specialized unit (20). There was, however, no difference between the two patient groups as regards their age or degree of neurological deficit on admission nor the prevalence of previous diseases. The aim to bring about a non-selected group of patients with stroke admitted to the SU was achieved.

Lumbar puncture with CSF spectrophotometry, skull X-ray, echoencephalography and brain scan were included in the investigation program in the SU and were consequently performed more often there than in the GMW. Arch angiographies were made as often in the GMW as in the SU, and were performed in the SU as the final investigation in patients considered for carotid endarterectomy (patients with TIA or a brain infarction with minor neurological deficits). In the GMW, arch angiography was not always a preoperative investigation but a diagnostic one, e.g. it had been performed in three patients older than 75 years and hardly considered for carotid endarterectomy, and in another four without prior CSF analysis. Criteria for angiography should be used to avoid unnecessary risks and the investigation is mainly to be regarded as preoperative.

A higher autopsy rate in the SU than in the GMW and a thorough clinical investigation secured a high reliability of the diagnoses in the SU and a distribution of diagnoses in good agreement with other authors (25). Contrary to this, more than one third of the GMW patients had a final diagnosis of ill-defined CVD before application of the diagnostic criteria of the SU, more than half (53%) of the patients had this diagnosis. These findings indicate that a discussion about criteria for diagnosis in different types of stroke should be of practical [illegible] It is possible that the high age of the p[illegible] and the lack of known efficient medical treatment in acute stroke influence negatively the [illegible] need of differentiation between cerebral infa[illegible] and haemorrhage. A more consequent use of [illegible] analysis would have diminished considerab[illegible] ill-defined stroke group in the GMW.

There was no difference in total hospital m[illegible]ty or length of hospital stay between the two p[illegible] groups. Although early rehabilitation and co[illegible]operation between different categories of th[illegible] sonnel were stressed in the SU, it must be re[illegible]bered that our SU is not an intensive care un[illegible] present finding of no difference in hospital m[illegible]ty between the SU and the GMW was exp[illegible] Some authors have reported that intensive c[illegible] stroke patients does not decrease hospital m[illegible] (7, 14, 16, 17, 20). Others have shown im[illegible]ments regarding the stroke patients' func[illegible] capacity by early intensive mobilization a[illegible]habilitation (1[illegible], 13, 15). It could not be eva[illegible] whether other such effects were achieved in o[illegible] since standardized assessments of the pa[illegible] functional capacity were not made conseque[illegible] the GMW during the study period.

Acute medical treatment with heparin [illegible]chaemic stroke was given somewhat more freq[illegible]ly in the SU than in the GMW. The thromb[illegible] infusion study carried out in some SU patien[illegible] brain infarction (5) was inconclusive and [illegible] hardly have influenced the outcome of th[illegible] SU [illegible]tients.

Secondary prophylactic treatment wi[illegible] ticoagulants and/or carotid endarterectom[illegible] been generally used as a prophylactic meas[illegible] embolism and TIA (9, 18, 19, 22) and treatmen[illegible] acetylsalicylic acid has been shown to be of va[illegible] men with TIA (6). Platelet aggregation inhib[illegible] anticoagulants were given to 85% of the SU [illegible] with a non haemorrhagic lesion in the SU a[illegible] 47% of the patients in the GMW. Howev[illegible] third of the latter had a diagnosis of ill-defined [illegible] e.g. anticoagulants had been given to som[illegible] without prior lumbar puncture. Although [illegible] neficial effects of these secondary prophy[illegible] measures still remain to be defined, it is prove[illegible] obvious that such treatment should not be [illegible] before a specific diagnosis of CVD has been [illegible]lished.

f computerized tomography is not available ıbar puncture with CSF spectrophotometry ›uld be used for differentiation between haemor ıgic and ischaemic cerebral lesions (21)

The following conclusions could be drawn from present study 1) An unselected and representa e group of patients with acute stroke was admit l to the SU 2) A higher frequency of ill defined 'D was seen in the GMW than in the SU A more ısequent use of spectrophotometry of CSF in tients treated in the GMW would have increased nsiderably the accuracy of diagnosis The better ality of diagnosis in the SU did result in a more quent and correct use of secondary drug ›phylaxis 3) Short term outcome did not differ tween patients treated in the SU and in the ıIW

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REFERENCES

von Arbin M Britton M de Faire U Helmers C Miah K & Murray V Validation of admission criteria to a stroke unit J Chronic Dis 33 215 1980

von Arbin M Britton M de Faire U Helmers C Miah K Murray V & Wester P O Strukturerad akutjournal för patienter med cerebrovaskulär sjukdom vid medicinklinik Opusc Med 23 91 1978

— A stroke unit in a medical department Organization and the first 100 patients Acta Med Scand 205 231 1979

— Erfarenheter från den cerebrovaskulära enheten vid Serafimerlasarettets medicinska klinik Lakartid ningen 76 2622 1979

Britton M de Faire U Helmers C Miah K & Rane A Lack of effect of theophylline on the outcome of acute cerebral infarction Acta Neurol Scand In press 1980

The Canadian Cooperative Study Group A randomized trial of aspirin and sulfinpyrazone in threatened stroke N Engl J Med 299 53 1978

7 Cooper S W Olivet J A & Wollsey F M Jr Establishment and operation of combined intensive care unit for patients with cardiac and cerebrovascular disease NY State J Med 72 2215 1972

8 Drake W E Jr Hamilton M J Carlsson M & Blumenkrantz J Acute stroke management and patient outcome the value of neurovascular care units (NCU) Stroke 4 933 1974

9 Fleming H A & Bailey S M Mitral valve disease systemic embolism and anticoagulants Postgrad Med J 47 599 1971

10 Frithz G & Werner I Studies on cerebrovascular strokes II Clinical findings and short term prognosis in a stroke material Acta Med Scand 199 133 1976

11 Haerer A F Smith R R & Currier R D The Mississippi regional medical program stroke unit Critique and follow up of the first 250 patients admitted South Med J 64 951 1971

12 Hewer R L Stroke units Br Med J 1 52 1972

13 Howard B E The clinical stroke team In Stroke diagnosis and management (ed W S Fields & S Moossy) p 98 Green St Louis 1973

14 Kennedy F B Pozen T J Gabelman E H Tuthill J E & Zaenthz S D Stroke intensive care—An appraisal Am Heart J 80 188 1970

15 McCann B C & Culbertson R A Comparison of two systems for stroke rehabilitation in a general hospital J Am Geriatr Soc 24 211 1976

16 Millikan C H Stroke intensive care units Objectives and results Stroke 10 235 1979

17 Norris J W & Hachinski V C Intensive care management of stroke patients Stroke 7 573 1976

18 Nunn D B Carotid endarterectomy an analysis of 234 operative cases Ann Surg 182 733 1975

19 Olsson J E Muller R & Berneli S Long term anticoagulant therapy for TIAs and minor strokes with minimum residuum Stroke 7 444 1976

20 Pitner S E & Mance C J An evaluation of stroke intensive care results in a municipal hospital Stroke 4 737 1973

21 Soderstrom C E Datortomografi och likvorspektrofotometri Två moderna diagnosmetoder vid cerebrovaskulära sjukdomar Thesis Stockholm 1978

22 Stanford J R Lubow M & Vasko J S Prevention of stroke by carotid endarterectomy Surgery 83 259 1978

23 Taylor R R Jr Acute stroke demonstration project in a community hospital J SC Med Assoc 66 225 1970

24 WHO International classification of diseases 1965 Revision WHO Geneva 1967

25 Wolf P A Dawber T R Thomas H E Colton T & Kannel W B Epidemiology of stroke Adv Neurol 16 5 1977

Vıtamın D Deficıency ın Welfare Instıtutıons for the Aged

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STRACT Serum concentratıons of 25 OH D ın a ıup of 47 elderly people (70–94 years old) lıvıng homes for the aged were lower than those ın a tched control group lıvıng ın their homes No dıf nces between the groups were noted in serum ızed calcıum alkalıne phosphatase ınorganıc ısphate, magnesıum or parathyroıd hormone The serum concentratıon of 25 OH D may be due to outdoor actıvıtıes and/or a smaller dıetary vıta D ıntake ın the ınstıtutıonalızed group The ıortance of preservıng an adequate vıtamın D us ın gerıatrıc patıents ıs emphasızed

words 25 hydroxyvıtamın D age ınstıtutıon

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ımın D deficıency ıs reported to be common ın rly especıally housebound and hospıtalızed ple Deficıent exposure to daylıght ıs con red to be the maın cause of vıtamın D deficıency he elderly (4 14) wıth malnutrıtıon (1) malab- ›tıon (2) and certaın drugs (8) as possıble con utory factors

'ıtamın D deficıency may convenıently be de ed by measurements of the vıtamın D metabo 25 OH D ın serum (15) Vır and Love (16) thus nd lower serum 25 OH D values ın ınstıtutıon ed elderly people than ın out patıents of the ıe age whıch ıs of consıderable ınterest wıth re ct to the care of gerıatrıc patıents

The aım of thıs study was to ınvestıgate ıf vıtamın deficıency exısts ın ambulant people lıvıng ın edısh ınstıtutıons for the aged The serum con ıtratıons of 25 OH D ıonızed calcıum total cal m alkalıne phosphatase phosphate magnesıum l parathyroıd hormone were determıned

SUBJECTS

study group comprısıng 24 women and 23 men (mean 84 range 70–90 years) was randomly selected from three homes for the aged Bedrıdden people and people wıth gastroıntestınal dısease such as partıal gastrıc resec tıon or who were on drugs known to affect vıtamın D status e g barbıturates and phenytoın were excluded Mınor dısabılıtıes such as arthrosıs vertıgo parkınsonısm and cardıac ıncompensatıon were accepted as well as ın take of frusemıde dıgoxın dıazepam paracetamol hy dralazıne propranolol and alumınıum hydroxıde All the subjects were ambulant

A reference group matched by age sex and general health status was selected from the Gerıatrıc Out Patıent Department All these subjects were lıvıng ın theır own homes

The study group and the control group were ınvestı gated at the same season (Aprıl and May) ın order to elımınate seasonal varıatıons ın vıtamın D metabolısm

METHODS

S 25 OH D was measured by competıtıve proteın bındıng assay accordıng to Bouıllon et al (3) wıth the modıficatıon that gelatıne was used ınstead of lıpoproteın ın order to dımınısh adsorptıon effects The coefficıent of varıatıon as determıned ıntra assay was 11 % at 20 nmol/l ($n=10$) and 12 % at 50 nmol/l ($n=14$) Correspondıng values as deter mıned ınterassay were 20 % at 20 nmol/l ($n=16$) and 15 % at 50 nmol/l ($n=26$) Lower lımıt of sensıtıvıty was 4 nmol/l Inorganıc phosphate and alkalıne phosphatase concentratıons ın serum were determıned wıth contınuous flow system on a SMAC ınstrument (Technıcon In struments Tarrytown NY) Serum ıonızed calcıum was analyzed wıth an ıon selectıve flow through system (Orıon SS 20 Orıon Research Cambrıdge Mass) (10) Serum magnesıum concentratıon was determıned by atomıc ab- sorptıon spectrometry and serum parathyroıd hormone concentratıon was analyzed accordıng to Kleerkoper et al (9) Tıme spent outdoors and the dıetary vıtamın D ın take durıng the last two days were estımated by dırect ınterview wıth the subject (12) Matched groups were ınterviewed on the same day

RESULTS

Mean values for vıtamın D ıntake and tıme spent outdoors were somewhat lower ın the study group than ın the reference group but the statıstıcal sıg

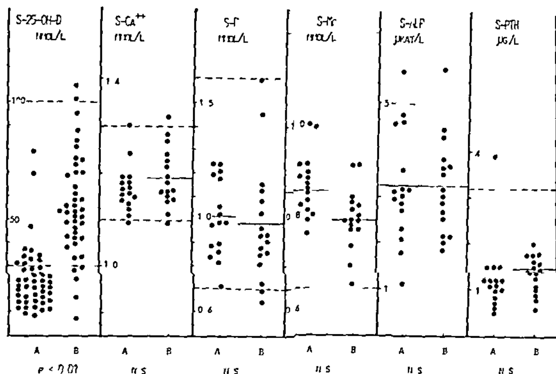


Fig 1 Biochemical findings in elderly people living in homes for the aged (*A*) and in people living in their own homes (*B*) —=Sample mean =normal range

nificance was difficult to validate as the available data were too imprecise

Determinations of 25 OH D levels revealed that the study group had lower values of this vitamin D metabolite than the control group ($p<0.01$) (Fig 1)

Certain other laboratory tests for variables known to be influenced by vitamin D deficiency serum ionized calcium inorganic phosphate magnesium alkaline phosphatase and parathyroid hormone were also carried out in a subgroup of 16 institutionalized subjects and 16 controls (Fig 1) No significant differences in these variables were detected between institutionalized and non institutionalized subjects Two of the 16 institutionalized subjects in this subgroup had had a fracture during the last 3 years while three fractures had occurred among the 16 controls

DISCUSSION

This study is a confirmation of the findings of Vir and Love (16) The subjects with low and normal S-25 OH D did not differ as regards alkaline phosphatase inorganic phosphate ionized calcium or parathyroid hormone concentrations Me ments of S 25 OH D are accordingly valuat revealing subclinical vitamin D deficiency teomalacia however can only be demonstrat histopathological examination which was no formed in this study It should be noted i context that bone fracture is a late sympt vitamin D deficiency whereas muscular weak fatigue and bone pain are more common but overlooked (13) As 16 of 47 subjects in the group had S 25 OH D values of less than 20 nn a level below which the frequency of osteoma is reported to be increased (5) vitamin D su ments might be of value This should be feasib MacLennon and Hamilton (11) observed peroral supplements did increase S 25 OH D i derly people and Coreless et al (7) found incre S 25 OH D concentrations in elderly people exposure to UV light

There are several possible reasons for the serum concentrations of 25 OH D observed in study Attempts to assess the duration of outd stay indicated that the institutionalized people less outdoor activities than the control group

r interview technique probably gave too impre se results for a definite conclusion Dietary differ ces between the two groups may also be respon ole for the low S 25 OH D level Malabsorption of tamin D reduced hepatic 25 hydroxylation or in eased vitamin D elimination may be additional ntributory factors

Thus we found low S 25 OH D in a group of nbulant elderly people living in homes for the aged it the biological significance of this observation s to be further elucidated

REFERENCES

Anwar M Nutritional hypovitaminosis D and the genesis of osteomalacia in the elderly J Am Geriatr Soc XXVI 309 1978

Barragry J M France W Corless D Gupta S P Switala S Boucher B J & Cohen R D Intestinal cholecalciferol absorption in the elderly and in younger adults Clin Sci Med Mol Med 55 213 1978

Bouillon R VanKerkhove P & De Moor P Measurement of 25 hydroxyvitamin D_3 in serum Clin Chem 22 364 1976

Challoner A V J Corless D Davis A Deane G H W Diffey B L Gupta S P & Magnus I A Personal monitoring of exposure to ultraviolet radiation Clin Exp Dermatol I 175 1976

Compston J E Horton L W L Laker M F Ayers A B Woodhead J S Clemens T L Fraher L & Pilkington T R E Bone disease after jejuno-ileal bypass for obesity response to oral hydroxyvitamin D^3 therapy In Vitamin D basic research and its clinical application (ed A W Norman K Schaefer Dv Herrath H G Grigoleit J W Coburn H F DeLuca E B Mawer & T Suda) p 1095 de Gruyter Berlin and New York 1979

6 Corless D Beer M Boucher B J Gupta S P & Cohen R D Vitamin D status in long stay geriatric patients Lancet I 1404 1975

7 Corless D Gupta S P Switala S Boucher B J Barragry J M Cohen R D & Diffey B L Response of plasma 25 hydroxyvitamin D to ultraviolet irradiation in long stay geriatric patients Lancet 2 649 1978

8 Hunter J Enzyme induction and medical treatment J R Coll Physicians Lond 8 163 1974

9 Kleerkoper M Ingham J P McCarthy S W & Posen S Parathyroid hormone assay in primary hyperparathyroidism Experience with a radioimmunoassay based on commercially available reagents Clin Chem 20 369 1974

10 Larsson L & Ohman S Serum calcium ion activity Some aspects on methodological differences and intraindividual variation Clin Biochem 12 138 1979

11 MacLennan W J & Hamilton J C Vitamin D supplements and 25 hydroxy vitamin D concentrations in the elderly Br Med J 2 859 1977

12 Marr J W Individual dietary surveys Purposes and methods World Rev Nutr Diet 13 105 1971

13 Morgan B Osteomalacia renal osteodystrophy and osteoporosis p 57 Thomas Springfield 1973

14 Preece M A Tomlinson S Tibot C A Pietrek J Korn H T Davies D M Ford J A Dunnigan M G & O Riordan J L H Studies of vitamin D deficiency in man Q J Med XLIV 575 1975

15 Stanbury S W & Mawer E B Physiological aspects of vitamin D metabolism in man In Vitamin D (ed D E M Lawson) p 305 Academic Press London New York and San Francisco 1978

16 Vir S C & Love A H G Vitamin D status of elderly at home and institutionalised in hospital Int J Vitam Nutr Res 48 123 1978

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Serum Reverse-T_3 Determinations in the Laboratory Diagnosis of Hyperthyroidism

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TRACT The relative discriminatory value of the ation of the serum reverse-T_3 levels for the lab ry diagnosis of hyperthyroidism was investi l in 47 patients with clinical signs or symtoms of rthyroidism The results were compared with from the determination of the total serum levels and T_4 prior and after correction for the bindig ins Twenty three of the patients had normal id function and 24 had hyperthyroidism The ation of the total serum T_3 level was superior to the determination of the total serum T_4 and rse T_3 levels even subsequent to correction for inding proteins

words reverse T_3 thyroxine triiodothyronine id function hyperthyroidism

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ı recent development of specific radioim oassays for determination of reverse T_3 now ı commercially available there has been con rable interest in the role of this compound in ous conditions (2 3 11) The relation between T_3 and reverse T_3 levels have been of special est It is not yet known if the reciprocal altera ın T_3 and reverse T_3 levels seen in different thyroidal diseases represent homeostatic at its at energy conservation by preferential T_4 adation to reverse T_3 rather than to T_3 or are ed by altered metabolic clerance The different ies have recently been summarized (1)

ıe clinical value of reverse T_3 determination for laboratory diagnosis of hypo and hyper oidism is not fully known The discriminatory er of reverse T_3 determination in patients with ible *hypo*thyroidism seems to be inferior to the rmination of TSH The reason is that a normal ; level excludes primary hypothyroidism while uch as 40% of hypothyroid patients have been reported to have reverse T_3 levels in the normal range (9) Reverse T_3 determinations in the labora tory diagnosis of *hyper*thyroidism have shown ele vated levels when compared to normals (1 4 7 9) Some of the hyperthyroid patients were found to have reverse T_3 levels in the normal range How ever the discriminatory power of reverse T_3 de termination for this diagnosis compared to the de termination of T_3 or T_4 levels before and after cor rection for the hormone binding proteins is unclear

The aim of the present investigation was to study the relative clinical value of reverse T_3 determina tions in patients with possible hyperthyroidism

STUDY POPULATION AND METHODS

In a recent investigation the discriminatory value of T_3 and T_4 determinations before and after correction for bind ing proteins and other functional tests were elucidated in 50 patients with clinical signs or symptoms of hyper thyroidism Each patient underwent a thorough clinical and laboratory investigation in order to establish the state of the thyroid function The results showed that 26 of the 50 patients had normal thyroid function and 24 had hyper thyroidism The study population laboratory methods and results have been reported (8) The reverse T_3 levels have now been analyzed in these patients Due to lack of serum three of the normals had to be excluded Re verse T_3 was determined by a commercially available kit (Hypolab S D Coinsins Switzerland) The reference in terval ($\pm$S D) was 0 34$\pm$0 10 nmol/l The T_3 uptake (T_3 U) test was performed using Sephadex as adsorbent (12) The free reverse T_3 index was calculated according to the formula for the free T_4 index (5) (reverse T_3) × (T_3U)/100

RESULTS

The mean levels and derived parameters of re verse T_3 T_3 and T_4 in the normal and hyperthyroid group are shown in Table 1 It can be seen that the mean levels in the normal and hyperthyroid group are clearly separated

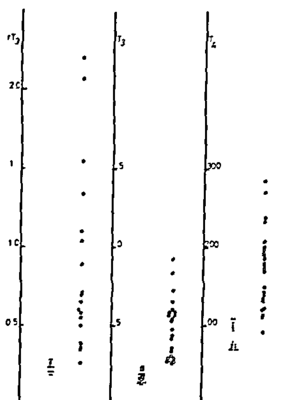


Fig 1 Serum levels of reverse T_3 (rT_3) T_3 and T_4 in the normal (●) and hyperthyroid patients (O)

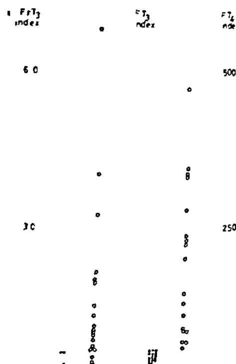


Fig 2 Derived parameters of rT_3 T_3 and T_4 lev normal and hyperthyroid patients Symbols as in

The levels of reverse T_3 T_3 and T_4 of the individual patients before and after correction for the influence of the binding proteins are shown in Figs 1 and 2 It can be seen that the determination of T_3 is superior to both the determination of T_4 and reverse T_3 for the laboratory discrimination between eu and hyperthyroidism Correction for the binding proteins slightly improved the separation of the two groups

The overlap in reverse T_3 levels between the normal and the hyperthyroid group indicates that the determination of reverse T_3 is not a suitable test as a discriminant between the two groups Similar conclusion can be made for the T_4 determination

DISCUSSION

Even if increased levels of reverse T_3 in hyperthyroidism have been described several objections to its clinical usefulness may be raised from the theoretical point of view One objection is that the monodeiodination of T_4 to reverse T_3 is increased during non thyroidal conditions like hep rhosis (4) acute febrile illness (10) mal and other systematic disorders with simulta decreased T_3 levels despite euthyroidism elevated reverse T_3 levels may be seen normal subjects

However the same objection regarding nostic usefulness could be raised for T_3 det tions as T_3 levels are simultaneously decrea der similar conditions Clinically the objecti not be of any major importance as the disc tory power of T_3 determinations is well esta for the routine laboratory diagnosis of thyroidism (14)

Other objections have been based upon th that reverse T_3 is derived from extrathyro deiodination and that only a minute amount duced by the thyroid (4 6) Thus the com does not necessarily reflect the function of thyroid gland (13) Furthermore reverse calorigenically inactive compound and may th rather inappropriate to determine for diagnos hypermetabolic condition (6)

le I rT_3 T_3 T_4 (nmol/l) and derived indices in euthyroid and hyperthyroid patients

	Euthyroid	Hyperthyroid
	23	24
+S D	0 26±0 18	0 91+0 76
e rT_3 index		
	19	19
+S D	0 28±0 19	1 71±1 59
	23	24
±S D	1 67±0 41	4 64±1 94
e T_3 index		
	19	19
±S D	1 79±0 29	7 78+4 91
	23	24
±S D	88 0±23 0	173 0±50 0
e T_4 index		
	19	19
±S D	94 8±18 8	281 5±128 8

ACKNOWLEDGEMENTS

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REFERENCES

Burman K D Recent developments in thyroid hormone metabolism Interpretation and significance of measurements of reverse T_3 3 3 T_2 and thyroglobulin Metabolism 5 615 1978

Burman K D Dimond R C Wright F D Earll J M Burton J & Wartofsky L A radioimmunoassay for 3 3 5 triiodothyronine (reverse T_3) J Clin Endocrinol 44 660 1977

Chopra I J A radioimmunoassay for measurement of 3 3 5 triiodothyronine J Clin Invest 54 583 1974

4 — An assessment of daily production and significance of thyroidal secretion of 3,3 ,5 triiodothyronine (reverse T_3) in man J Clin Invest 58 32 1976

5 Clark F & Horn D B Assessment of thyroid function by the combined use of the serum protein bound iodine and resin uptake of J^{131} triiodothyronine J Clin Endocrinol 25 39 1965

6 Gavin L Castle J McMahon F Martin P Hammond M & Cavalieri R R Extrathyroidal conversion of thyroxine to 3 3 5 triiodothyronine (reverse T_3) and to 3 5 3 -triiodothyronine (T_3) in humans J Clin Endocrinol 44 733 1977

7 Hufner M Grussendorf M & Knopfle M Gehalt an 3 3 5 T_3 (reverse T_3) im Plasma bei verschiedenen Funktionszustanden der Shilddruse Acta Biol Med Germ 37 447 1978

8 Kallner G Kågedal B Ljunggren J G & Tryselius M Clinical value of total T_4 and T_3 determinations in patients with suspect hyperthyroidism before and after correction for binding proteins Acta Med Scand 204 369 1978

9 Kaplan M M Schimmel M & Utiger R D Changes in serum 3 3 5 triiodothyronine (reverse T_3) concentrations with altered thyroid hormone secretion and metabolism J Clin Endocrinol 45 447 1977

10 Ljunggren J G Kallner G & Tryselius M The effect of body temperature on thyroid hormone levels in patients with non thyroidal illness Acta Med Scand 202 459 1977

11 Nicod P Burger A Staeheli N & Vallotton M B A radioimmunoassay for 3,3 5 triiodo-L thyronine in unextracted serum J Clin Endocrinol 42 823 1976

12 Nosslin B A simplified technique for the triiodothyronine test (T_3-test) with Sephadex Scand J Clin Lab Invest (Suppl) 17 177 1965

13 Smallridge R C Wartofsky L Desjardins R E & Burman K O Metabolic decrease and production rates of 3 3 5 triiodothyronine in hyperthyroid euthyroid and hypothyroid subjects J Clin Endocrinol 47 345 1978

14 Tryselius M Kallner G & Ljunggren J G Comparison between serum thyroxine and triiodothyronine estimation and the TRH test in the routine diagnosis of hyperthyroidism Acta Med Scand 201 263 1977

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Report on a Patient with Watery Diarrhoea Syndrome Caused by a Pancreatic Tumour Containing Neurotensin, Enkephalin and Calcitonin

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ISTRACT A patient with watery diarrhoea syn ome (WDS) is described A pancreatic tumour was ind containing many cells with immunoreactivity enkephalin and neurotensin a few with im inoreactivity to calcitonin but none to vasoactive estinal peptide (VIP) High levels of calcitonin, irotensin VIP and pancreatic polypeptide (PP) e present in plasma as measured by radioim noassay After removal of the tumour, the plasma els of the first three peptides returned to normal l the WDS disappeared On the other hand, plasma did not change No specific symptoms could be at buted to the new spectrum of peptides found in tumour This is the first report of a pancreatic nour containing high levels of neurotensin

v words watery diarrhoea VIP neurotensin enke ilin calcitonin PP pancreatic tumour

ta Med Scand 208 95 1980

e *watery diarrhoea* syndrome (WDS) first de ibed in 1958 (49) is characterized by intractable tery diarrhoea hypokalaemia impaired glucose erance and an islet cell tumour of non β-cell e It has been suggested that the syndrome is ised by tumours producing vasoactive intestinal lypeptide (VIP) (4 40) However the disease has n described in patients with normal VIP values t increased levels of calcitonin gastrin glucagon retin (41) prostaglandin (28) and pancreatic lypeptide (PP) (31) Since many of the tumours in 'ients with WDS secreted more than one peptide ias been difficult to define the one responsible for specific symptoms of this syndrome

A patient with WDS and pancreatic tumour containing neurotensin enkephalin and calcitonin is described The clinical and laboratory findings with this new spectrum of hormone overproduction are reported

PATIENT REPORT AND RESULTS OF SPECIAL STUDIES

The patient a 65 year-old man had always enjoyed good health apart from a thyroidectomy because of atoxic colloid goiter 20 years ago He was receiving substitution therapy with 75 mg of a desiccated thyroid preparation daily His mother also suffered from goiter but otherwise there were no endocrine diseases in the family history

During the last 1 5 years before admission the patient had observed periods of gradually increasing watery diarrhoea with up to 15 urgent calls to stool per day and faecal volumes exceeding one litre per day No mucus or blood was observed in the stool During these attacks he often experienced minute-long flushes localized to head and trunk but no nausea or vomiting In the last six months he had lost 15 kg in weight and suffered from muscular weakness There were no symptoms of gastritis respiratory depression kidney failure or polyuria nor any mental changes or general analgesia

All haematological indices and liver function tests were normal Fasting blood glucose was 11 5 potassium 3 0 sodium 135 calcium 3 3 phosphate 1 2 mmol/l Creatinine was normal Serum thyroxine and triiodothyronine two months after withdrawal of thyroid substitution were normal Administration of 200 μg TRH was however not followed by any increase in TSH

Abbreviations WDS = watery diarrhoea syndrome VIP = vasoactive intestinal peptide PP = pancreatic polypeptide

Table I *Polypeptide content (pmol/l) in plasma and presence of immunoreactive cells in the tumour*
NTLI = neurotensin-like immunoreactivity PPLI = PP-like immunoreactivity VIPLI = VIP-like immunoreactivity

Polypeptide	Normal range in plasma	Preoperative plasma	Peroperative tumour	Postoperative plasma
Calcitonin	120–290	5 000	+	160
NTLI	<600	3 200	+	24 5
PPLI	<400	1 400	+	1 300
VIPLI	<20	250	–	3 5

Calcified tissue was demonstrated on X ray in the right lobe of the thyroid gland Scintigraphy showed a normal [131]I uptake and distribution A fine needle biopsy yielded normal tissue Urinary excretion of norepinephrine epinephrine 4-hydroxy 3 metoxymandelic acid and 5 hydroxyindolic acetate before and during diarrhoea attacks were normal

Plasma growth hormone prolactin glucagon LH FSH insulin and testosterone were all normal Serum gastrin was within the normal range The secretion of gastric acid was low before and after pentagastrin stimulation (6 μg/kg b wt) Determination of calcitonin like neurotensin like PP like and VIP like immunoreactivity showed markedly increased values in plasma (Table I)

The patient s mild diabetes was controlled by diet alone The hypercalcaemia normalized upon rehydration The hypokalaemia was corrected by 4 5 g KCl p o daily The watery diarrhoea responded only moderately to opiates but no effect of indomethacin 100 mg/day (an inhibitor of prostaglandin synthesis) was observed A computerised tomogram revealed a tumour in the caudal part of the pancreas despite a negative angiography

At *surgery* a solid encapsulated tumour (5×5×4 cm) was resected with a distal pancreatectomy No metastases were found at operation The diarrhoea flushing muscular weakness and hypokalaemia subsided However the patient developed hypertension postoperatively (210/110 mmHg) He was back at work after eight weeks and soon regained normal body weight

Fasting blood glucose levels were normal on a regular diet but the i v glucose tolerance test showed a decreased *K* value (0 80) The unresponsiveness to TRH remained unaltered Plasma calcitonin neurotensin and VIP-like immunoreactivity were normal one month and six months after the operation but the PP values remained raised (Table I)

METHODS

Radioimmunoassays

All blood samples for peptide and hormone assays were collected in chilled glass test tubes Trasylol® (Bayer Leverkusen) was added (10% of volume) to inhibit proteolysis The samples were centrifuged at 4°C and the plasma was frozen Plasma for PP and VIP assays was freeze-dried and stored at −70°C VIP was analyzed as described previously (20) PP was determined using a phase radioimmunoassay procedure (32) PP antise well as pure human PP for standards were gifts from Chance Eli Lily Minneapolis

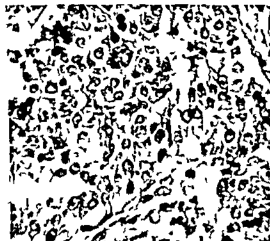
The methods used for radioimmunoassay of neuro sin will be presented in detail elsewhere and only a b description of the method is given here The antise (0–7701) was raised in rabbits and reacted with neuro sin (NT) NT (1–12) (Gln[4]) and (Gln[4]) NT (1–11) b with NT (4–13) or smaller C terminal fragments of It showed no cross reactivity with gastrin inhib polypeptide porcine VIP porcine secretin choler kinin 33 cholecystokinin 34 cholecystokinin 39 creatic glucagon species substance P insulin somatostatin bovine pancreatic polypeptide am bombesin gastrin 17 gastrin 34 or with trypsiniz trin 34 which presumably contains the N terminal decapeptide Neurotensin like immunoreactivity in plasma from the patient eluted from a Sep column as a single peak Calcitonin human GH glucagon insulin testosteron FSH LH and p were analyzed by radioimmunoassay

Histopathological and immunohistochemical analyses

Thin tumour slices were fixed in 10% buffered fo +4°C for 12 or 24 hours The fixed specimens wer rinsed over night in a phosphate buffer with 5% Cryostat sections 10 μm thick were processed ac to the indirect immunofluorescence technique of (12) Other tissue samples were embedded in paraf dehydration and clearing in xylene Paraffin μm thick were stained with haematoxylin-eosin cessed for argentaffin (43) with argyrophil techniq 25 43) Sections were also stained with the peroxidase technique (46)

The following antisera were used on the cryos tions for somatostatin (no R141 C) (16) gastrin (no (38) VIP (no 5603 7) (17) substance P (K25) neurotensin (8 29) serotonin (45) and methionine phalin (no 336) (42) Two insulin antisera (a gift Wide) glucagon (50) and bovine PP (24) were used f deparaffinized sections

The calcitonin antibody was raised in rabbits after jugation of synthetic human calcitonin to bovine albumin In both immunohistochemical techniques the sections were incubated with antisera at +4°C f hours according to Goldman (21)



1 Tumour cells with mainly solid arrangement and ng slight polymorphism Many tumour cells contain oplasmic vacuoles often located to the capillary pole of the cell HE ×350



2 (A) Immunofluorescence micrographs of the pan ic tumour Many cells exhibiting strong neurotensin immunoreactivity can be seen (B) A subpopulation of kephalin immunoreactive cells in the adjacent section rs indicate 50 μm

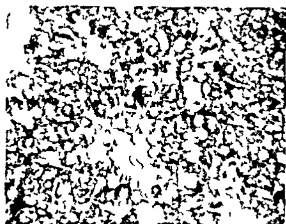


Fig 3 Section from the tumour stained with calcitonin antiserum (PAP technique)

Histology and immunohistochemistry

The tumour cells mainly showed a solid arrangement with multifocal necroses In most areas the stroma was fairly richly vascularized but contained sparse strands of connective tissue Most of the tumour cells contained a moderate amount of weakly eosinophilic stained cytoplasm In many the cytoplasm contained vacuoles of varying size often concentrated to the capillary of the cell Most nuclei showed only a slight pleomorphism but some giant nuclei were seen In some areas the nuclei contained prominent nucleoli Very few mitoses were observed (Fig 1)

Almost all tumour cells displayed argyrophilia with the Grimelius stain indicating their endocrine nature With the Sevier Munger technique the staining reaction varied in different parts of the tumour in some areas the majority of cells showed argyrophil reaction while in others only few cells were stained No silver positive reaction was observed with the Masson and the Hellerstrom–Hellman techniques indicating absence of serotonin and somatostatin respectively

The tumour contained cells with immunoreactivity to neurotensin methionine-enkephalin and calcitonin A few PP immunoreactive cells were also seen In some areas the majority of cells showed neurotensin like immunoreactivity (Fig 2) In the same areas a minority of cells were enkephalin immunoreactive but it was not possible to determine if the same cells showed immunoreactivity with both antisera Groups of cells showing calcitonin immunoreactivity occurred in other areas of the tumour where no neurotensin or enkephalin reactivity could be demonstrated (Fig 3)

None of the other antisera tested including VIP antiserum revealed any immunoreactive cells Furthermore there were areas in the tumour with argyphilic cells which did not show any immunoreactivity at all

DISCUSSION

No single etiological agent which could be responsible for the WDS has been established so far VIP

Table II *Normal localization pharmacophysiological effects and observed clinical symptoms of peptides found in the tumour and serum of the patient*

Peptide	Localization	Ref no	Effects: Pharmacophysiological	Effects: Clinical	Ref no
Calcitonin	C-cells in thyroid calcitonin cells in pancreatic endocrine tumours	37	Ca/s ↓ Mg/u ↑ stimulate small intestinal juice production	Diarrhoea*	13 22
Enkephalin	Many areas of the brain except the pituitary Highest conc in antrum duodenum pancreas ileum gallbladder and lesser amounts in colon	36	Opiate like central nervous system effects respiratory depression increased gastric motility Central vasomotor depression release of ADH prolactin	Euphoria analgesia flush* constipation emesis hypotonia*	1 14 ˙ 3? 47 .
Neurotensin	Ileal mucosa less in the jejunum traces in the stomach duodenum and colon Hypothalamus and other areas of the brain	10 40	Inhibition of intestinal motility vasodil in small intestine Vasoconstriction in adipose tissue Inhibition of gastric acid secretion Stimulation of glucagon release Inhibition of insulin release enhancement of glycogenolysis Role in postprandial processes	Diabetes inhibited gastric acid secretion* hypotonia*	2 3 9 11 33
PP	At the periphery of pancreatic islets in pancreatic acinar tissue few cells in the duodenum	20	Stimulates basal acid secretion inhibits pentagastr stimulated Enhances secretin-induced pancreatic secretion (low dose) inhibits stimulated pancreatic secretion (high dose)	Diarrhoea* inhibited gastric acid secretion	19 31
VIP	Widely distributed throughout the gastrointestinal tract from lower oesophagus duodenum to the colon and rectum as well as in the pancreas Nervous tissues e g as mesent ganglia submucous and myenteric plexus of intest wall cerebrovascular and genital organ nerves	7	Stimulates small intestinal secretion. Inhibits gastric acid production Relaxes gallbladder Stimulates pancreatic secretion Vasodilatory agent lowers blood pressure Disturbs glucose and calcium metabolism	Diarrhoea* flushing attacks* diabetes hypercalcemia inhibited gastric acid secretion* hypotonia*	4 5

* Symptoms present in our patient

has been present in excessive amounts in many patients (6) but not in all (26) The novel finding in our subject with a typical WDS was the demonstration of a new spectrum of peptides in the pancreatic tumour including neurotensin enkephalin and calcitonin VIP could not be demonstrated in the tumour cells while high levels of the peptide were found in plasma

The symptoms in our patient can be accounted for by the known effects of VIP alone (Table II) although some symptoms could also be related to the other peptides The raised plasma glucose low gastric acid secretion may have been du[e] high neurotensin level which has been sho[wn] exert such effects on rats (2 9) The discrep[ancy] between the high VIP level in the blood and the [lack] of ability to demonstrate VIP-producing cells [in the] tumour is probably due to technical difficult[ies] the immunohistochemical procedure VIP c[ould] also have been released from sites outside [the] tumour by substance(s) produced in it. Calc[itonin] probably an unlikely candidate for such a ro[le]

ents with diarrhoea and high calcitonin levels to medullary thyroid carcinoma recently were id to have normal levels of VIP in the cir tion (34) The effects of enkephalin and rotensin on VIP in plasma are still unknown In context it was of special interest that Grimelius ning technique showed cells in the tumour that not stain with any of the antibodies used

he persisting high PP values after surgery could due either to some other tumour not observed far or to hyperplasia of islet PP cells *outside* tumour tissue as described by Larsson (30) patients with endocrine pancreatic tumours ents with diabetes mellitus have been found to e raised PP levels which correlate with the level blood glucose (19) Normalization of blood ose in our subject and still persisting high val of PP make this aetiology less probable

he development of hypertension after surgery ords with previous findings in similar patients This may be a prolonged rebound effect after nalization of the VIP levels when the tumour been removed

patient has been described with WDS and a reatic tumour containing immunoreactivity to phalin neurotensin and calcitonin In addition levels of VIP were also found but only in the ma This is the first time that neurotensin has n demonstrated in a pancreatic tumour How neither neurotensin nor enkephalin alone d explain the florid collection of symptoms id in this patient

REFERENCES

Alumets J Falkmer S Grimelius L Håkansson R Lundberg O Sundler F & Wilander E Immunocytochemical demonstration of enkephalin and β-endorphin in endocrine tumours of the rectum A survey of 27 colo-rectal carcinoids Acta Pathol Microbiol Scand (A) In press 1980

Andersson S Chang D Folkers K & Rosell S Inhibition of gastric acid secretion in dogs by neurotensin Life Sci 19 367 1976

son S Rosell S Hjelmquist U Chang D Folkers K Inhibition of gastric and intestinal motor activity in dogs by (Gln⁴)-neurotensin Acta Physiol Scand 100 231 1977

Barraclough M A & Bloom S R Vipoma of the pancreas Observations on the diarrhoea and cir ulatory disturbances Arch Intern Med 139 467 1979

Bloom S R Vasoactive intestinal peptide the major mediator of the WDHA (pancreatic cholera) syndrome Value of measurement in diagnosis and treatment Dig Dis 23 373 1978

6 — VIP and watery diarrhoea VI In Gut hormones (ed S R Bloom) p 583 Churchill Livingstone Edinburgh and London 1978

7 Bloom S R & Polak J M Gut hormone overview In Gut hormones (ed S R Bloom) p 3 Churchill Livingstone Edinburgh and London 1978

8 Brown M Rivier J Kobayashi R & Vale W Neurotensin like and bombesin like peptides CNS distribution and actions In Gut hormones (ed S R Bloom) p 550 Churchill Livingstone Edinburgh and London 1978

9 Brown M & Vale W Effects of neurotensin and substance P on plasma insulin glucagon and glucose levels Endocrinology 98 819 1976

10 Buchan A M Polak J M Sullivan S Bloom S R Brown M & Pearsel G E Neurotensin in the gut In Gut hormones (ed S R Bloom) p 544 Churchill Livingstone Edinburgh and London 1978

11 Carraway R Demers L M & Leeman S E Hyperglycemic effect of neurotensin a hypothalamic peptide Endocrinology 99 1452 1976

12 Coons A H Fluorescent antibody methods In General cytochemical methods (ed J F Danielli) p 399 Academic Press London 1958

13 Doepfner N & Briner U Inhibition of gastric secretion and ulcer formation with synthetic solomon calcitonin in animal experiment Triangle 16 105 1977

14 Donovan B T The behavioural actions of the hypothalamic peptides a review Psychol Med 8 305 1978

15 Ebeid A M Murray P D & Fischer J E Vasoactive intestinal peptide and the watery diarrhoea syndrome Ann Surg 187 411 1978

16 Efendic S Nylén A Roovete A & Uvnas Wallensten K Effects of glucose and arginine on the release of immunoreactive somatostatin from the isolated perfused rat pancreas FEBS Lett 92 33 1978

17 Fahrenkrug J & Schaffalitzky de Muckadell O B Radioimmunoassay of vasoactive intestinal polypeptide (VIP) in plasma J Lab Clin Med 89 1379 1977

18 — VIP and watery diarrhoea III In Gut hormones (ed S R Bloom) p 576 Churchill Livingstone Edinburgh and London 1978

19 Floyd J C Human pancreatic polypeptide In Clinics in endocrinology & metabolism (ed K D Buchanan) p 379 Saunders Philadelphia 1979

20 Gepts W Baetens D & DeMey J The PP cell In Gut hormones (ed S R Bloom) p 229 Churchill Livingstone Edinburgh and London 1978

21 Goldman M Fluorescent antibody methods Academic Press London 1978

22 Gray T K Bieberdorf F A & Fordtran J S Thyreocalcitonin and the jejunal absorption of calcium water and electrolytes in normal subjects J Clin Invest 52 3084 1973

23 Grimelius L A silver nitrate stain for A_2 cells of human pancreatic islets Acta Soc Med Upsalien 73 243 1968

24 Hallgren R Lundqvist G & Chance R E Serum levels of human pancreatic polypeptide in renal disease Scand J Gastroenterol 12 923 1977
25 Hellerström C & Hellman B Some aspects of silver impregnation of the islets of Langerhans in the rat Acta Endocr (Kbh) 36 518 1960
26 Holst J J Gut endocrine tumour syndromes In Clinics in endocrinology & metabolism (ed K D Buchanan) vol 8 p 413 Saunders Philadelphia 1979
27 Hughes J & Kosterlitz H W The enkephalins endogenous peptides with opiate receptor agonist activity Neuroregulations Psychological Disorders p 329 University Press Wolf City Texas 1977
28 Jaffe B M & Condon S Prostaglandins E and F in endocrine diarrheagenic syndromes Ann Surg 184 516 1976
29 Kobayashi R M Brown M & Vale W Regional distribution of neurotensin and somatostatin in rat brain Brain Res 126 584 1977
30 Larsson L I PP-producing and mixed endocrine pancreatic tumours In Gut hormones (ed S R Bloom) p 605 Churchill Livingstone Edinburgh and London 1978
31 Larsson L I Schwartz T Lundqvist G Chance R E Sundler R Rehfeld J F Grimelius L Fahrenkrug J Schaffalitzky de Muckadell O B & Moan N Occurrence of human pancreatic polypeptide in pancreatic endocrine tumours Possible implication in the watery diarrhoea syndrome Am J Pathol 85 675 1976
32 Lundberg J M Hamberger B Schulzberg M Hökfelt T Granberg P O Efendic S Terenius L Goldstein M & Luft R Enkephalin and somatostatin-like immunoreactivities Occurrence in adrenal medulla and pheochromocytoma of man Proc Natl Acad Sci USA 76 4079 1979
33 Nagai K & Frohman L A Hyperglycemia and hyperglucagonemia following neurotensin administration Life Sci 19 273 1976
34 Öberg K Loof L Bostrom H Grimelius L Fahrenkrug J & Lundquist G Calcitonin in patients with Verner Morrison syndrome Scand J Gastroenterol In press 1980
35 Polak J M Sullivan S N Bloom S R Buchan A M J Facer P Brown M R & Pearse A G E Specific localization of neurotensin to the cell in human intestine by radioimmunoassay and immunocytochemistry Nature 270 183 1977
36 Polak J M Sullivan S N Buchan A M J Bloom S P Facer P Hudson D & Pearse A G E Endorphins In Gut hormones (ed S R Bloom) p 501 Churchill Livingstone Edinburgh and London 1978
37 Ramband J C Nisard H Calmette C M... M S Hill P A & Besterman H Hy... citoninaemia in vipomas Lancet 1 220 1978
38 Rehfeld J F Stadil F & Rum B Produc... evaluation of antibodies for the radioimmuno... gastrin Scand J Clin Lab Invest 30 221 197...
39 Rosell S Burcher E Chang D & Fol... Cardiovascular and metabolic action of ne... and (Gln[4])-neurotensin Acta Physiol Scand... 1976
40 Said S I & Faloona G R Elevated pla... tissue levels of vasoactive intestinal polype... the watery-diarrhoea syndrome due to pa... bronchogenic and other tumours N Engl... 293 155 1975
41 Schmitt M G Soergel K H Hensley ... Chey W Y Watery diarrhoea associated w... creatic islet cell carcinoma Gastroenterolog... 1975
42 Schultzberg M Lundberg J M Hök... Terenius L Brandt J Elde R & Golds... Enkephalin-like immunoreactivity in gland ... nerve terminals of the adrenal medulla Neur... 3 1169 1978
43 Sevier A C & Munger B L A silver m... paraffin sections of neural tissue J Neuropa... Neurol 24 130 1965
44 Singh I A modification of the Masson... method for staining argentaffin cells A... 115 81 1964
45 Steinbusch H Verhofstad A & Joos... Localization of serotonin in the central nerv... tem by immunocytochemistry Neuroscienc... 1978
46 Sternberger L A Immunocytochemistry ... Hall Englewood Cliffs 1974
47 Stubbs W A Delitala G Jones A Jeffc... J Edwards C R W Ratter S J Besser... Bloom S R & Alberti K G M Hormo... metabolic responses to an enkephalin anal... normal man Lancet 2 1225 1978
48 Verebey K Volauka J & Clovet D End... in psychiatry Arch Gen Psychiatry 35 877 1...
49 Verner J V & Morrison A B Islet cell ... and a syndrome of refractory watery diarrh... hypokalemia Am J Med 117 374 1958
50 Wilander E Portela-Gomes G Grimel... Lundquist G & Skoog V Enteroglucag... substance P like immunoreactivity in argenta... argyrophil rectal carcinoids Virchows Arch... Pathol) 25 117 1977

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Preoperative Localization of Aldosterone-Producing Adenomas

An Analysis of the Efficiency of Different Diagnostic Procedures Made from 11 Cases and from a Review of the Literature

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CT The efficiency of six different methods lable for topographical diagnosis of primary al eronism was analysed in retrospect from 11 sur lly verified cases and by an analysis of 360 cases rted in the literature Differentiation between rplasia and adenoma was most safely predicted ionitoring the diurnal rhythm of plasma aldo- ne and its reaction to posture Adrenal vein eterization with aldosterone determinations was ul in establishing the presence of hyperplasia in oximately 70% of these cases Correct localiza of aldosterone producing adenomas was made in than 90% by vein catheterization while veno- hy and radio-cholesterol scintigraphy had lower ostic accuracy It is therefore suggested that mination of plasma aldosterone both by vein terization and by peripheral monitoring should ised ahead of other diagnostic procedures for graphical examinations in primary aldoste sm

words aldosterone [131]I cholesterol scintigram terization

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ary aldosteronism (PA) is a primary cause of blood pressure in less than 1% of patients with rtension (20) A correct diagnosis of this syn ne is however of great importance since the opriate therapy leads to improvement or per ent cure from the hypertensive and metabolic equences of aldosterone hypersecretion

he diagnosis of PA is usually established with difficulties thanks to widely available sensitive specific methods for determination of aldoste and renin The major problem at present is to out the morphological substrate for the disease ateral or bilateral adenoma or bilateral hy lasia Several diagnostic methods are being for this purpose Thus angiographic examina tions of adrenal arteries or veins have been used over more than decades (7 8 24) [131]Iodine-choles terol scintigram was introduced by Conn s group in 1971 (6) and was thereafter modified by simultane ous administration of dexamethasone (36) as well as by the introduction of new iodine cholesterol com pounds (23 33) Determination of aldosterone in plasma sampled from the adrenal veins was de scribed by Bucht et al in 1964 (4) and has since then been extensively used (7 14 16 29 35 39 42) Finally it has been suggested that the pattern of the diurnal rhythm of plasma aldosterone as well as the effect of posture on plasma aldosterone would be of value for the distinction between hyperplasia and tumour (1 15 19 34)

The aim of the present study was to evaluate the efficiency of the above diagnostic procedures for the localization of aldosterone producing adrenal tumours and for the non operative distinction be tween tumours and hyperplasia

PATIENTS AND METHODS

Patients

Unilateral adrenalectomy due to PA was performed in 11 subjects in 1975–78 at the Karolinska Hospital Stock holm All had a history of hypertension (1–19 years) and hypokalemia The diagnosis was established by the de monstration of a low plasma renin activity (PRA) together with a high urinary excretion of aldosterone not suppress ible by exogenous administration of mineralocorticoids (Table I) In ten of the subjects a typical adrenal tumour was removed at surgery followed by correction of hypokalemia and by improvement of or cure from hyper tension In one subject (no 1) no tumour was found at operation Adrenalectomy was performed on the left side and the microscopic examination revealed a diffuse

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Abbreviations PA = primary aldosteronism CT = com puter tomography PRA = plasma renin activity

Table I *Relevant data on the patients*

Case no	Age (y)	Sex	Duration of hypertension (y)	BP (mmHg)	Lowest serum K+ (mmol/l)	Recumbent/upright PRA (pkat/l)	Urinary aldosterone excretion basal/during Florinef* (nmol/day)	PAD
1	67	♂	12	240/135	2 8	0 07/0 22	85/100	Hype
2	58	♀	9	205/110	2 9	0 04/0 04	100/90	Aden
3	55	♀	16	215/110	2 2	0 01/0 01	55/50	Aden
4	54	♀	18	210/110	2 8	0 02/0 04	55/60	Aden
5	52	♀	19	200/110	2 2	0 04/0 04	140/170	Aden
6	50	♀	15	240/140	1 8	0 04/0 04	205/120	Aden
7	48	♂	7	235/140	3 1	0 02/0 05	115/115	Aden
8	41	♀	11	220/115	2 4	0 01/0 01	55/60	Aden
9	39	♀	5	180/110	2 2	0 02/0 02	160/140	Aden
10	38	♂	1	185/125	2 9	0 04/0 10	145/120	Aden
11	22	♀	2	180/105	2 3	0 02/0 02	105/85	Aden

* Mineralocorticoid suppression test was performed over four days with fludrohydrocortisone (Florinef®) in a d. of 0 4 mg Aldosterone levels on the last day of the test are given

hyperplasia of the zona glomerulosa Hypokalemia and hypertension persisted in this case after the operation

Diagnostic methods

Adrenal arteriography aortography and celiac arteriography were performed in nine cases (24) Adrenal venography was performed in all 11 cases Catheterization was done with a preformed radiopaque catheter Only A P projections were used

In connection with venography but prior to the complete injection of contrast medium blood samples were collected from caval and left adrenal veins for determination of aldosterone and cortisol When possible samples were also drawn from the right adrenal vein

^{131}I cholesterol scintigrams were carried out by a slight modification of the method described by Seabold et al (36) In order to block the isotope uptake in the thyroid gland we have given both levothyroxine 0 2 mg daily (Levaxin ® Nyegaard Oslo Norway) and Lugol s solution for 14 days prior to isotope administration Dexamethasone 2 0 mg daily (Dexacortal ® Organon Oss Holland) was given for nine days except for cases 2 3 and 11 who received steroids for three days only The adrenal uptake of radioactivity was counted by a gammascintillator at three and seven days after the isotope injection

Computer tomography (CT) was performed in five cases A Delta scanner with an exposure time of 150 sec was used in four of them In case 7 CT was done by a General Electric 7800 with an exposure time of 5 6 sec

The diurnal rhythms of aldosterone and cortisol were assessed by venous blood sampling at 06 12 16 22 and 02 hours Plasma aldosterone was determined according to Poulsen et al (32) and cortisol by a fluorometric method (30)

RESULTS

Adrenal arteriography (Table II)

Adrenal arteriography was performed in eight subjects with unilateral adenoma The adrenals were visualized on both sides in four patients and side in two In two cases the adrenals w visualized Thus the procedure was tec successful in 10 of 16 examined adrenal gla the hyperplasia patient arteriography r normal adrenals Out of six tumours in a adequately visualized at arteriography on were seen whereas two were too small to tected by this method

Adrenal venography (Table II)

The left adrenal was visualized in all ten p with unilateral tumour while the right adren mapped out in five of them Four out of six tu in the left adrenal gland and one out of four right were visualized at venography Those ing detection were small ones (cases 7 and 1 patient 9 a large tumour was found on the side In this patient however, venography a dicated a tumour on the left side Full remiss hypertension and potassium depletion foll removal of the right adrenal gland proved th left sided lesion was not an aldosterone pr ing tumour Thus in this patient the venogr examination gave false positive information l patient with hyperplasia venography disclo normal adrenal gland at the left side catheterization of the right adrenal vein failed

^{131}I cholesterol scintigram (Table III)

Adrenal scintigrams during dexamethasone pression were carried out in all patients Th rect localization was achieved in seven pat

: II *Localization of adrenal tumours by adrenal angiography*
not visualized NP = not performed

Venography		Arteriography		Findings at exploration	
sin	dx	sin	dx	Approximate tumour weight (g)	Localization of tumour
Tumour	Normal	Tumour	NV	2	sin
Normal	NP	Normal	Tumour	8	dx
Tumour	NP	Tumour	NV	3	sin
Normal	NP	NV	NV	4	dx
Normal	NP	Normal	Tumour	10	dx
Normal	Normal	NP	NP	1	sin
Tumour	NP	NP	NP	1	sin
Tumour	Tumour	NV	NV	6	dx
Tumour	Normal	Normal	Normal	<1	sin
Normal	Normal	Normal	Normal	<1	sin

nostic results

	No of angiographies performed			
	10	5	8	8
rect	7	5	4	4
e positive	1			
e negative	2		2	
nclusive			2	4

ı adenoma In two cases (nos 8 and 19) no ope uptake was registered and in case 7 bilateral ope uptake of similar magnitude was seen In patient with hyperplasia the scintigram indi d correctly bilateral autonomous aldosterone duction (11)

nputer tomography

. of four adenoma patients examined by CT the iour was detected in only one (no 6) who had largest tumour (Table II) Though the tumour of e 3 was quite large it was not identified by CT the subject with hyperplasia the adrenals ap- red normal on CT

enal vein catheterization (Table IV)

is investigation was performed in eight patients h adenoma and in the patient with hyperplasia case 7 the procedure was repeated after one nth The left adrenal vein was successfully plored in all investigations while adequate blood nples were obtained from the right side on only occasions

Cortisol in samples from vena cava varied between 120 and 880 nmol/l and in those from adrenal veins from 220 to 9 270 nmol/l In general the plasma cortisol levels were several times higher in adrenal than in systemic blood There was not significant difference between cortisol levels in samples

Table III *Isotope uptake in adrenals during* ^{131}I *cholesterol scintigram*
− = No uptake + = slight uptake ++ = high uptake

Pat no	Isotope uptake in adrenals		PAD
	sin	dx	
1	+	+	Hyperplasia
2*	++	+	Adenoma sin
3	−	++	Adenoma dx
4	+		Adenoma sin
5	−	++	Adenoma dx
6	−	++	Adenoma dx
7	+	+	Adenoma sin
8	−	−	Adenoma sin
9	−	++	Adenoma dx
10	−	−	Adenoma sin
11	++	+	Adenoma sin

* *Dexamethasone administration for three days only*

Table IV Plasma levels of aldosterone (pmol/l) and cortisol (nmol/l) measured at certain places in venous system by gentle catheterization

Subj no	Left adrenal vein			Right adrenal vein			Vena cava			PAD
	Aldo sterone	Cor tisol	Ratio[a]	Aldo-sterone	Cor tisol	Ratio[a]	Aldo-sterone	Cor tisol	Ratio[a]	
1	4 770	1 780	2 7			–	2 170	410	5 1	Hyperpla
2	44 000	750	59 3	7 000	9 270	0 8			–	Adenoma
3	600	740	0 8			–	1 300	360	3 6	Adenoma
6	1 700	750	2 3			–	8 500	270	31 5	Adenoma
7[b]	7 600	340	22 5			–	2 000	530	3 8	Adenoma
7[b]	80 000	3 000	26 3			–	1 800	490	3 7	Adenoma
8	24 000	5 980	4 1			–	2 000	880	2 3	Adenoma
9	4 400	1 850	2 4	83 000	2 370	37 2			–	Adenoma
10	8 700	1 370	6 3			–	5 300	790	6 7	Adenoma
11	18 000	610	29 3	500	220	2 2	600	120	5 0	Adenoma

[a] Calculated as $\frac{\text{p aldosterone (pmol/l)}}{\text{p-cortisol (nmol/l)}}$

[b] Catherized on two occasions

from the adrenal veins of five normal glands (2 570 ±1 700 nmol/l mean ± S E M) and from six tumours (2 070±750 nmol/l) indicating that the cortisol secretion measured locally by crude sampling was not changed by the presence of an aldosterone producing tumour

In the three adenoma cases in whom a successful bilateral catheterization was performed (nos 2 9 and 11) 6–20 times higher aldosterone levels were found in plasma sampled from the adrenals with tumours In the other five adenoma patients a comparison was made between the aldosterone levels in the left adrenal vein and the caval vein In cases 3 and 6 the levels in the caval vein were much higher than in the left adrenal vein which strongly suggested hypersecretion of aldosterone from the right adrenal In cases 7 8 and 10 aldosterone levels were higher in the left adrenal vein than in the caval vein In all these patients the adenoma was found in the left adrenal gland In patient 7 the aldosterone level in the left adrenal vein was almost ten times higher during the second than the first catheterization whereas the ratio between aldosterone and cortisol was almost the same This suggests that a quotient between aldosterone and cortisol may offer a better estimation of the true secretion of aldosterone

In the subject with bilateral hyperplasia only the left adrenal vein was catheterized The aldosterone/cortisol ratio for this subject was higher in caval vein than in the left adrenal vein suggesting high secretion of aldosterone from the right adrenal Thus in this case the diagnosis of hyperplasia c not be established by venous sampling alone

Diurnal rhythm and effect of posture on peripheral plasma aldosterone and cortisol levels (Table V)

In all eight subjects examined plasma aldoste at 6 a m was clearly above the normal range 272 pmol/l) while plasma cortisol was within normal range (276–828 nmol/l) The seven aden patients and the patient with hyperplasia had a ly normal diurnal rhythm of cortisol and ald rone with nadir concentrations in the late a noon and a rise in the concentrations during t morning hours The effect of posture on ald rone secretion was analysed by comparing peripheral concentrations in recumbent positi 6 a m with those at noon i e after at least hours in the upright position A fall in plasma al sterone was noticed in all cases with PA du adenoma In the patient with bilateral hyperpl (no 1) a rise in plasma aldosterone was ins seen upon posture

Efficiency of diagnostic procedures analysed review of 360 operated cases of PA reported in the literature (Table VI)

In 38 reports during recent years 452 pati ... PA have been presented A unilateral adenoma found in 309 of the 360 operated cases In (...

..le V Diurnal variation in plasma cortisol (nmol/l) and aldosterone (pmol/l) in patients with PA due to lateral adenoma or hyperplasia

subjects were in recumbent position between 22 p m and 08 a m

	Measured at				
	06 a m	12 00	16 p m	22 p m	02 a m
..erplasia					
Cortisol	490	340	190	60	130
Aldosterone	612	837	879	403	153
..lateral adenoma					
Cortisol	410	420	500	190	260
Aldosterone	1 570	620	510	120	1 0?0
Cortisol	427	176	99	187	127
Aldosterone	693	471	388	388	444
Cortisol	529	309	151	85	309
Aldosterone	4 051	943	888	1 637	3 108
Cortisol	490	380	180	170	170
Aldosterone	1 084	456	346	363	640
Cortisol	436	356	356	179	140
Aldosterone	1 359	471	610	249	693
Cortisol	570	470	190	220	220
Aldosterone	1 986	1 786	858	1 648	1 889
Cortisol	402	187	201	121	55
Aldosterone	1 387	610	471	555	388

..se 309 the affected side was denoted in the ..ort concerned Thus 61% of the tumours were ..alized to the left side A total of 101 cases were ..nsidered to have bilateral hyperplasia However ..only 48 subjects this diagnosis was verified by ..roscopic examination As to the adenomas only ..gically verified cases were included in the calcu..ons In the hyperplasia cases however it was .. always possible to exclude microscopically un..ified cases since the reports do not regularly give ..h information

..Although no group of workers has used all the ..gnostic methods applied in our study some ..ups had compared the diagnostic value of two or ..ee methods Thus in patients with adenoma the ..rect tumour localization was usually best pre..ted by estimating the plasma aldosterone con..tration in the adrenal vein by adrenal vein ..heterization procedures in spite of the fact that ..th adrenal veins were successfully catheterized in ..s than 50% of the cases (14 21 29 35 36 39 Thus the diagnostic efficiency of this method ..a tumour localizer was excellent predicting the ..ect side in 93% of the cases In cases with ..ateral hyperplasia the accuracy of this method was somewhat lower a correct diagnosis being pre dicted in about 74% of the cases

Adrenal venography has been extensively used and at least some groups of researchers have ob tained very good results Thus Conn et al (8) have reported a correct tumour localization in 32 out of 38 adenoma cases However this method has given less satisfactory results according to other inves tigators This is mainly due to the difficulties to catheterize the right adrenal vein As to the sum marized experience with venography a correct diagnosis was predicted in about 62% of the cases It is notheworthy that here too one false positive result has been reported (21)

Adrenal radio cholesterol scintigraphy was origi nally introduced in 1971 by Conn s group (6) In 1976 they reported on their results with this method in 16 patients with unilateral adenoma and five with bilateral hyperplasia Based on mainly the same subjects Seabold et al (36) demonstrated a unilat eral isotope accumulation in about 80% of the adenomas In contrast to these reports Fukuchi and Nakajima (14) Helber et al (17) and Yune et al (42) have reported on a much lower diagnostic effi ciency in adenoma cases As to patients with

Table VI *Survey of 360 operated PA cases collected from the literature*

		Adenoma correctly localized by				Hyperplasia correctly localized by			
Authors	Year	Veno graphy	Cathe teriza tion	Radio choles terol scinti graphy	Decrease in plasma aldoste rone in upright position[b]	Veno graphy	Cathe teriza tion[a]	Radio choles terol scinti graphy	Dec in p ald ron upr pos
Balikian et al (1)	1968	–	–	–	0/3	–	–	–	–
Britton et al (3)	1976	1/2	2/2	2/2	–	–	–	–	–
Clarke et al (5)	*1979*	2/7	7/7	5/6	2/4	0/1	1/1	0/1	0 1
Conn et al (7 8)	1972–76	32/38	–	c	–	–	–	c	–
Dige Petersen et al (9)	1975	–	–	2/3	–	–	–	–	–
Espiner et al (11)	1976	5/7	6/10	–	–	–	–	–	–
Fromantin et al (13)	1977	0/3	3/3	1/1	–	–	–	–	–
Fukuchi et al (14)	1976	7/22	18/23	19/27	–	–	–	–	–
Ganguly et al (16)	1973	–	7/7	–	9/11	–	2/4	–	0/
Helber et al (17)	1975	–	–	3/5	–	–	–	–	–
Hogan et al (18)	1976	–	–	8/8	–	–	–	–	–
Horký et al (19)	1976	–	4/4	–	4/4	–	2/2	–	0/
Horton & Finck (21)	1972	8/12	12/12	–	–	2/2	2/2	–	–
Mantero et al (26)	1976	–	–	–	5/5	–	–	–	0
Melby et al (28)	1967	3/7	7/7	–	–	–	–	–	–
Mitty et al (29)	1973	6/10	8/8	–	–	–	–	–	–
Ohbuchi & Murakami (31)	1976	–	–	–	7/9	–	–	–	–
Sarkar et al (33)	1977	4/4	4/4	4/4[f]	–	1/4	4/5	5/5[e f]	–
Schambelan et al (34)	1976	–	–	–	6/6	–	–	–	0/
Scoggins et al (35)	1972	3/10	10/10	–	–	–	–	–	–
Seabold et al (36)	1976	11/14	9/9	10/13 15/16[h]	–	1/4	3/3	1/5 5/6[h]	–
Sundsfjord et al (37)	1974	–	–	2/2	–	–	–	–	–
Vetter et al (40)	1974–76	–	9/9	8/9	2/5	–	0/2	0/2	0/
Wiggins et al (41)	1976	–	4/4	–	–	–	–	–	–
Yune et al (42)	1976	8/10	8/8	3/8[h]	–	–	–	–	–
Correct information of total no of investigations (%)		62	93	79 75[h]	74	–	74	–	–

[a] Blood taken from adrenal vein(s) for analysis of aldosterone and cortisol concentrations
[b] Peripheral blood samples taken in the morning (recumbent) and at noon (upright position)
Patients included in the report by Seabold et al
[d] Two of reported cases verified by surgery
One of reported cases verified by surgery
[f] ^{131}I-6β-iodomethyl 19 nor-cholesterol scintigraphy performed with dexamethasone suppression
[g] Diagnosis not confirmed by surgery
[h] Performed under dexamethasone suppression

hyperplasia Conn et al (7) and Seabold et al (36) have reported on a high diagnostic efficiency by this method This has however not been confirmed by other investigators (17 42) Thus based on the present experience as calculated from the literature ^{131}I-cholesterol scintigraphy gives false positive information in more than 20% of the investigations

Several groups have reported on a parallelism between the diurnal rhythms of cortisol and aldosterone in patients with PA due to adenoma while such a parallelism was not seen in hyperplasia (15 22, 26, 31 39) Moreover Ganguly et al reported that plasma aldosterone concentration reduced in the majority of adenoma cases af few hours in upright position compared with hormone levels in recumbency In contrast changed or even increasing plasma aldost concentrations were registered in hyper cases These observations have later on been firmed by several investigators (19 26 31 33 According to these reports no single subject

:rplasia (12 verified by surgery) exhibited a ural fall in plasma aldosterone concentration e this was seen in 77% of adenoma cases In :nts with PA due to adenocarcinoma Seabold (36) have reported on a correct localization of umour in one case with venography and adre vein catheterization while radio cholesterol igram did not visualize the metastatic masses have observed one case of PA due to a meta : adrenal carcinoma in our clinic Interestingly iis case the metastases did not accumulate pes enough to make their localization possible he very few carcinoma cases studied so far ma aldosterone levels did not show diurnal hm or postural decrease (34 39)

DISCUSSION

'der to choose the best therapy for patients with a correct topographical diagnosis and differen on between adenoma and hyperplasia is neces

The current opinion considers surgery unwar ed in patients with bilateral hyperplasia who ild receive medical treatment with spironolac : or other drugs On the other hand in patients i adenoma the surgical removal of an aldoste : producing tumour leads to normalization of 'd pressure in about 70% of the cases (25)

he ideal method to solve the problems of topo hical diagnosis in PA should be relatively inex sive and associated with as little discomfort or erse reactions for the patients as possible thermore it should answer the two important stions 1) *Bilateral or unilateral adrenal dis* :? 2) In cases with unilateral disease to later : the tumour Since numerous diagnostic pro- ures have been used in most reports on this i one could envisage that this ideal method is lacking

'f the *radiologic methods adrenal venography* been most commonly used and some groups e reported on correct lateralization in 70–80% in s with unilateral adenoma In our opinion 'ever the problems associated with catheteriza i of the right adrenal vein makes this method ful in only a limited *number of cases Furth* adrenal venography is potentially danger as the rapid injection of contrast medium in 10% of patients leads to an extravasal con t leakage (27) This complication was also ed in two of our cases though not associated with a serious outcome Occasional infarction of an adrenal tumour may be fortuitously provoked in this way (12) and infarction of both adrenal glands producing adrenal insufficiency has been reported in at least two patients (10 38)

Thus morbidity after venography is not in frequent and even fatal outcome has been reported in one case (3) Another problem with radiological methods is that the demonstration of a tumour in a PA patient does not prove that the lesion is an aldosterone producing adenoma Thus in accor dance with Horton and Finck (21) and in one of our cases a tumour was seen in one adrenal without evidence of an enhanced steroid hormone produc tion from this gland

Adrenal arteriography has not been extensively used in patients with PA From our experience the diagnostic efficiency of this method is not encourag ing probably because most tumours causing PA are too small to allow identification Thus inconclusive results are to be expected in 30–50% of the cases examined with arteriography It is therefore our impression that adrenal arteriography should be used only if other diagnostic procedures have failed

The radio cholesterol methods for visualization of the adrenals have received much enthusiasm Our experience as well as that of some other groups indicates however that a correct lateraliza tion is obtained in approximately more than 70–80% of the patients This method is not free from complications either In one of our cases the rela tively long dexamethasone period had to be discon tinued due to a florid psychosis a few *days after the* start of steroid administration

There is no doubt that adrenal vein catheteriza tion is superior to other methods in cases with uni lateral tumours Thus when both adrenal veins are successfully catheterized the correct topographic *diagnosis can be safely predicted However for* technical reasons the right adrenal vein is difficult to catheterize In most cases the interpretation has therefore to rely on blood samples taken from the left adrenal vein and from the inferior vena cava Two major problems are associated with this in *terpretation Firstly in our study* as well as in other studies (16 28 41) there was an obvious overlap in the absolute concentrations of aldosterone in the adrenal vein from tumours hyperplastic and even normal glands Secondly secretory bursts of al dosterone and cortisol from a diseased or normal

gland can occur during catheterization Since no evidence is at hand demonstrating altered cortisol secretion in hyperplastic or tumorous glands an improvement of the diagnostic precision can be achieved by calculating the ratio between plasma concentrations of aldosterone and cortisol This is also demonstrated by us as well as by others (35) The ratio adrenal vein aldosterone to cortisol may therefore be of critical value when the catheterization procedure is successful on one side only

The adrenal vein catheterization procedure allows no complete differentiation between PA due to adenoma or hyperplasia It should also be noticed here that bilateral tumours have been found in about 10% of PA and that the differentiation from hyperplasia by vein catheterization in such a case will be very difficult In many cases a discrimination between patients with adenoma and hyperplasia can be obtained by studying the postural effect on peripheral plasma levels of aldosterone and PRA Although hyperplasia was found in only one of our patients our findings were in good agreement with those of previous investigators Thus in this patient an increase in the plasma aldosterone concentration was noticed after posture while the hormone levels decreased in most of our adenoma cases Also the PRA in this patient was slightly increased at standing up while no such effect was seen in the adenoma cases

Therefore a correct preoperative topographic diagnosis can be made in most patients with PA with the adrenal vein catheterization procedure together with an analysis of plasma aldosterone in recumbent and upright position In our opinion other diagnostic procedures such as adrenal venography arteriography and radio cholesterol scintigraphy are of a more limited value Furthermore the use of these methods is associated with adverse reactions Therefore they should be used as diagnostic procedures only in patients in whom catheterization and peripheral hormone monitoring have failed Computer tomography may be valuable in cases with large tumour masses i e malignant tumours Most benign aldosterone producing tumours seem too small to allow detection by this new method

REFERENCES

1 Balikian H M Brodie A H Dale S L Melby J C & Tait J F Effect of posture on the metabolic clearance rate plasma concentration and blood production rate of aldosterone in man *J Clin Endocr Metab 28* 1630 1968
2 Baylis R I S Edwards O M & Storer F C... plications of adrenal venography Br J Radiol 43 ... 1970
3 Britton K E Goodwin T J Peart W S & S... M E Adrenal aldosterone producing adenoma ... of colonic potential in diagnosis and subtraction s... ning technique for localization Br Med J 2 11 ...
4 Bucht H Bergström J Lindholmer B W... H & Hokfelt B Catheterization of the left ad... vein for contrast injection and steroid analys... cases of Conn s syndrome Acta Med Scand ... 233 1964
5 Clarke D Wilkinson R Johnsson I D A H... ing P M & Haggith J W Severe hypertensi... primary aldosteronism and good response to sur... Lancet I 483 1979
6 Conn J Beierwaltes W H Liberman L M... san A N Cohen E L Bookstein J J & He... K R Primary aldosteronism Preoperative tu... visualization by scintillation scanning J Clin E... crinol Metab 33 713 1971
7 Conn J W Cohen E L & Herwig K R ... dexamethasone modified adrenal scintiscan ... poreninemic aldosteronism (tumor versus h... plasia) A comparison with adrenal venograph... adrenal venous aldosterone J Lab Clin Me... 841 1976
8 Conn J W Morita R Cohen E Beirwalte... H McDonald W J & Herwig K R Prima... dosteronism Arch Intern Med 129 417 1972
9 Dige Petersen H Munkner T Fogh J Bl... Toft M & Lund J O ^{131}J 19 iodocholesterol ... tigraphy of the adrenal cortex Acta Endocrinol ... 80 81 1975
10 Eagan R T & Page M I Adrenal insuffic... following bilateral venography JAMA 215 115 1...
11 Espiner E A Jameson J B Perry E G & M... K Adrenal venography and sampling in the diag... and treatment of primary aldosteronism NZ M... 83 313 1976
12 Fisher E E Turner F A & Horton R Remo... of primary hyperaldosteronism after adrenal v... graphy N Engl J Med 285 334 1971
13 Fromatin M Gaulier D Pailler J L & Rig... D Reflexions sur la valeur des differentes ex... plorations dans le diagnostic topographique du s... drome du Conn Ann Endocrinol (Paris) 38 159 ...
14 Fukuchi S & Nakajima K Comparative stud... diagnosis for location of adrenal adenoma in pat... with primary aldosteronism Folia Endocrinol J... 52 1046 1976
15 Ganguly A Dowdy A J Luescher J A ... Melada G A Anomalous postural response ... plasma aldosterone concentration in patients wi... dosterone producing adrenal adenoma J Clin En... crinol Metab 36 401 1973
16 Ganguly A Melada G A Luescher J A & Do... dy A J Control of plasma aldosterone in prim... aldosteronism Distinction between adenoma a... hyperplasia J Clin Endocrinol Metab 37 765 197...

Helbe A Dvorak K W nkelmann W Meurer K A Wurz H & D ckmans A [3] J-Cholesterin Szin graph e der Nebenn ere Dtsch Med Wochen schr 100 ,574 1975
Hogan M J McRae J Schambelan M & B gl en E G Locat on of aldosterone produc ng adenomas w h [13] J 19-iodocholesterol N Engl J Med 794 410 1976
Ho ky K Gregorova I S l kova Malkova E & Vancura J D fferent al d agnos s of pnmary and pseudoprimary hyperaldosteron sm Rev Czech Med — 181 1976
Horton R Aldoste one Rev ew of its phys ology and d agnostic aspect of primary aldosteron sm Metabol sm 77 1575 1973
Horton R & F'nck E D agnos s and local zat on n primary aldosteron sm Ann Intern Med 76 885 197?
Kem D C We nberger M H Gomez Sanches C H ggins J R & Kramer N J The role of ACTH n the epi od c release of aldosterone in pat ents w th idiopath c adrenal hyperplas a hypertens on and hyperaldosteron sm J Lab Cl n Med 88 761 1976
Kojma M Maeda M Ogawa H N tta K & Ito T Homoallul c rearrangement of 19 odocholesterol J Chem Soc Chem Commun 2 47 1975
Lindvall N & Slezak P Arteriography of the ad renals Rad ology 97 999 1969
Lins P E Adamson U & Efend S A follow up study n primary aldosteron sm Acta Med Scand To be publ shed
Man ero F G on M Armanin D & Opocher G Aldosterone regulat on n primary aldosteron sm d f ferences between adenoma and b lateral hyperplas a Clin Sc Mol Med 51 379 1976
Melby J C Solv ng the adrenal les on(s) of primary aldosteronism N Engl J Med 794 441 1976
Melby J C Spark R F Dale S L Egdahl R H & Kahn P C D agnos s and localizat on of aldosterone produc ng adenomas by adrenal ve n cath e enzat on N Engl J Med 777 1050 1967
M ty H A N col s G L & Gabrilove J L Ad renal venography cl n cal roentgenograph c cor relat on n 80 pat ents Am J Roentgenol 119 564 1973
de Moor P Steeno O Rask n M & Hendrik A Fluorometric de erm nat on of free plasma 11 hyd o-corticostero ds in man Acta Endocrinol (Kbh) 33 297 1960
Ohbuch S & Murakam T Secretory regulat on and ep sod c secret on of aldosterone n pat ents w th primary aldosteron sm Fol a Endocrinol Jpn 5? 1191 1976
3? Poulsen K Sancho J & Haber E A s mplif ed rad o mmunoassay for plasma aldosterone employ ng an antibody of un que spec f city Cl n Immunol Im munopathol 7 373 1974
33 Sarkar S D Cohen E L Be erwaltes W H Ice R D Cooper R & Gold E N A new and superior adrenal imaging agent [3] J-6β Jodomethyl 19 nor cholesterol (NP 59) Evaluat on in humans J Clin Endocr nol Metab 45 353 1977
34 Schambelan M Brust N L Chang B C F Sla ter K L & B gl en E G C rcad an rhythm and effect of posture on plasma aldosterone concentration in primary aldosteron sm J Cl n Endocrinol Metab 43 115 1976
35 Scoggins B A Odd e C J Hare W & Coghlan J P Preoperat ve lateral sat on of aldosterone produc ing tumours n primary aldosteronism Ann Intern Med 76 891 197?
36 Seabold J E Cohen E L Be erwaltes W H H nerman D L N sh yama R H Bookste n J J Ice R D & Balachandran P Adrenal imaging with J 19 Jodocholesterol in the d agnost c evaluation of pat ents w th aldosteron sm J Cl n Endocrinol Metab 4? 41 1976
37 Sundsfjord J A Norman N & Jørgen en H Ad renal sc nt graphy n primary aldosteronism Acta Med Scand 195 15 1974
38 Taylor H C & Sa hs C R Primary aldosteron sm Rem ss on and development of adrenal insuff c ency after adrenal venography Ann Intern Med 85 207 1976
39 Vetter H Vetter W Beckerhoff R Sabbe A Nussberger J W tassek F & S egen haler W Primarer Aldosteron smus D agnose Se ten lokal sat on und Regula on der Hormonsekret on Schweiz Med Wochenschr 105 1695 1975
40 Vetter W Vetter H Beckerhoff R W ttasek F Poul ad s G Furrer J & S egenthale W Endo krine Hyperton e be primarem Aldosteron smus und be Cush ng Syndrom Schweiz Med Wochenschr 106 1773 1976
41 W ggins R Jawett T Loose H & Slater J D H Adrenal venous aldosterone and cort sol concen trations n primary hyperaldosteronism Proc Soc En docrinol 69 3? 1976
4? Yune H Y Klatte E C Grim C E Weinbe ger M H Donohue J P Yum M N & Wellman H N Rad ology n primary aldosteron sm Am J Roentgenol 1?7 761 1976

Amyloid Deposits in Bone Marrow Aspirates in Primary Amyloidosis

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STRACT Amyloid deposits aspirated from the ıe marrow have a characteristic appearance in y-Grunwald-Giemsa stained smears, and al t specific fibrillar pattern when viewed in an elec ı microscope

words amyloidosis bone marrow findings
ı Med Scand 208 111 1980

re seems to be some disagreement in the litera as to the frequency of finding amyloid in bone row aspirates from patients with primary loidosis Hallen and Rudin (3) studied 18 pa ts with proven primary amyloidosis and did not amyloid at histological examination of the bone row in any of them Neither are amyloid de its in the bone marrow mentioned in some of the ling textbooks of haematology nor pictured in ıe of the foremost haematological atlases On other hand Conn and Sundberg (2) described showed microphotos of amyloid in bone row aspirates in 4 out of 5 patients with amy osis and Kyle et al (4) found amyloid in bone row smears in 16 out of 66 patients

/e have recently seen a large number of amyloid osits in bone marrow aspirates from two pa ts with primary amyloidosis

CASE REPORTS

1

ıale born in 1923 was admitted to hospital in Feb with a more than 5 years history of back pain His ht had reduced from 172 cm at age 20 to 161 cm in and roentgenograms had shown severe osteoporosis several compression fractures of the vertebrae

Laboratory findings on admission Urinalysis was normal ESR (Westergren) 49 mm/hour Hb 13 9 g/100 ml RBC 4 6 mill /µl WBC 5 100/µl platelets 175 000/µl Serum concentrations of calcium 2 4 mmol/l (normal 2 2-2 6) phosphorus 1 2 mmol/l (normal 0 9-1 4) creatinine 89 µmol/l (normal 71-124)

Total serum proteins were 71 g/l and serum electrophoresis was normal Bone marrow aspirate liver biopsy and aspirated subcutaneous fat all showed amyloid deposits Test for serum amyloid A related protein was negative The bone marrow aspirate showed on the average 4% mature looking plasma cells A diagnosis of primary amyloidosis was made

Case 2

A female born in 1918 was admitted to hospital in Nov 1975 because of lassitude and proteinuria

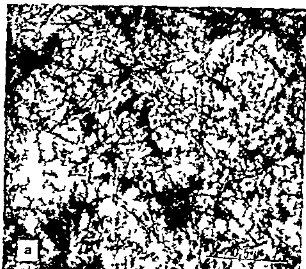
Laboratory findings Urinalysis showed moderate proteinuria 2 7 g/l ESR (Westergren) 133 mm/hour Hb 11 2 g/100 ml RBC 4 0 mill /µl WBC 6 400 platelets 282 000/µl Serum concentrations of calcium 2 2 mmol/l phosphorous 1 5 mmol/l creatinine 146 µmol/l

Total serum proteins were 59 g/l Serum electrophoresis showed albumin of 20 g/l There was a monoclonal component of about 10 g/l in the beta-gamma region Immune electrophoresis showed the monoclonal component to be IgA lambda

Agarose and immunoelectrophoresis of the urine showed moderate non selective proteinuria which included polyclonal IgG and small amounts of IgA lambda Bence Jones proteinuria was not found Bone marrow aspirate and renal biopsy showed amyloid deposits The bone marrow aspirate showed 10% somewhat immature plasma cells and renal biopsy showed some tubular casts of lamellar appearance A diagnosis of myelomatosis with amyloidosis was made

MATERIALS AND METHODS

Light microscopy Films from bone marrow aspirate were fixed in absolute methanol and then stained by May Grunwald-Giemsa at pH 6 8



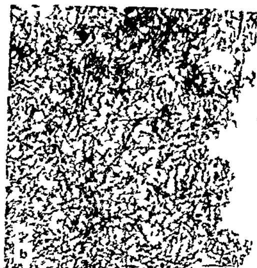


Fig 2 Electron microscopic section from bone marrow of case 1 (*a*) and case 2 (*b*) showing the characteristic meshwork of amyloid fibrils

Electron microscopy The bone marrow aspirate was fixed in 2 5% glutar aldehyde in 0 1 M phosphate buffer pH 7 2-7 4 for 2 hours and postfixed in 1% osmium tetroxide in Tyrode solution pH 7 4 for 1 hour Dehydration was carried out in graded ethanols and the specimen was embedded in Epon 812 The sections were cut with an LKB Ultramicrotome stained with lead citrate and uranyl acetate and examined in a Siemens El mikroskop 1 electron microscope

RESULTS

Light microscopy The bone marrow smears from case 1 showed a large number and from case 2 a moderate number of pink to-purple waxy to transparent irregularly shaped masses These masses which often surrounded and incorporated a large number of bone marrow cells might have with a hasty glance been mistaken for ordinary marrow particles In some places the masses did not incorporate any bone marrow cells and then had a quite characteristic appearance (Fig 1*b* colour plate) The marrow of case 1 contained 4% mature plasma cells and of case 2 10% somewhat immature plasma cells

Electron microscopy At a magnification of about 60000 we could see a meshwork of fibrils with a width of approximately 7 5–10 nm (Fig 2) This appearance is typical for amyloid deposits

DISCUSSION

Our patient 1 had severe osteoporosis and in [illegible] ways resembled a patient described by Axel[illegible] al (1) Our patient showed large amou[illegible] amyloid deposits in all bone marrow aspira[illegible] the sternum as well as from the iliac crest [illegible] were about 4% plasma cells in the bone ma[illegible] without signs of immaturity Test for serum [illegible] loid A related protein was negative A diagn[illegible] primary amyloidosis was made Patient 2 [illegible] nephrotic syndrome monoclonal IgA lambda [illegible] serum and 10% somewhat immature plasma [illegible] in the bone marrow A diagnosis of [illegible] myeloma with amyloidosis was made

The appearance of amyloid deposits in [illegible] stained bone marrow smears has been ap[illegible] scribed by Conn and Sundberg (2) A str[illegible] less homogeneous purple to pink staining [illegible] material occurring in masses or clouds amo[illegible] marrow cells The masses of amyloid are [illegible] discrete or occur in association with clus[illegible] cells fat or fragments of vessels Isolated ma[illegible] amyloid give a distinctive cumulus cloudlike [illegible] appearing light and transparent near the edg[illegible] more dense and billowy near the center" Th[illegible] scription fits well also our cases

In our patients the electron microscop[illegible] showing a meshwork of typical amyloid f[illegible] proved that the structure less pink to-purple

the bone marrow really were amylo d de

th nk that it is important to become aware of ıaracteristic appearance of amyloid deposits mes found in smears from bone marrow aspı In some cases it may (perhaps unexpected come an important lead towards the correct os s and may explain an otherwise puzzl ng hological find ng

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REFERENCES

1 Axelson U Hallen A & Raus ng A Amylo dosis of bone J Bone Jo nt Surg (Br) 5? 717 1970
2 Conn R B & Sundberg R D Amylo d d sease of the bone marrow Am J Pathol 38 61 1961
3 Hallén J & Rud n R Peri collagenous amylo dos s Acta Med Scand 179 483 1966
4 Kyle R A Pease G L R chmond H & Sull van L Bone marrow asp rat on in the antemortem d ag nos s of primary system c amylo dos s Am J Cl n Pathol 45 ?5? 1966



Fig 1a Plasma cells showing some irregularities in the cytoplasm which perhaps correspond to concentric lamellar bodies (May–Grunwald–Giemsa)



Fig 1b Smear of bone marrow aspirate showing amyloid desposits (May–Grunwald–Giemsa)

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Abnormal Pattern of the Rough Endoplasmic Reticulum of Plasma Cells in Multiple Myeloma ıth Multiple Concentric Lamellar Bodies and "Single Sac Loops"

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TRACT A patient with IgG myeloma showed a ıly abnormal pattern of the rough endoplasmic ɔulum (RER) with multiple concentric lamellar es and ' single sac loops This abnormal pattern ıt be due to either a complete rearrangement of ırchitecture within the cell and/or a pathology ın vall of the sacs of RER

words myeloma abnormal RER pattern

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ıs (1) quoted a number of different types of ɔlogy of the rough endoplasmic reticulum R) reported in multiple myeloma In most ın es a fairly large number of pathological plasma are reported in a particular patient Most pa s with multiple myeloma have a well developed but occasionally it may be represented by a few lamellae and has a more lymphoid ap- ance

aldonado et al (3) and later Tanaka and Good (4) described various patterns of RER in mul myeloma lamellar tubular concentrically nd the nucleus lamellar tubular concentrically not around nucleus or vesicular instead of lar In some cases the tubules or vesicles would ıoderately or markedly distended The marked stended sacs of the RER may contain soluble ns which appear as flaming in plasma cells ɔlid proteins appearing as Russel bodies when ed with May Grunwald Giemsa (1)

e have recently observed a pattern of multiple ntric lamellar bodies and single sac loops in R of the plasma cells in a patient with multi a

CASE REPORT

The patient was a female born in 1918 In Dec 1974 she had a transitory febrile period lasting for a few days Her family doctor found an increased ESR which remained elevated around 120 mm/hour Serum electrophoresis in Feb 1975 showed a monoclonal gammopathy

The patient was admitted to the Section of Haematolo gy Medical Department A Rikshospitalet on April 22 1975 On admission she was moderately pale otherwise normal findings Laboratory findings ESR 135 mm/hour Hb 9 7 g/100 ml leukocytes 2 6×10⁹/l platelets 238×10⁹/l blood There were 20% plasma cells in the bone marrow Total serum proteins were 110 g/l A large monoclonal (IgG kappa) component was found in the gamma region and gamma globulins were 49 g/l No osteolytic lesions were observed Serum creatinine was normal

The patient was treated with melphalan and responded *The total proteins decreased gradually to 78 g/l in Oct* 1976 with a gammaglobulin concentration of 20 g/l She relapsed again and in Aug 1977 the total proteins were 124 g/l gammaglobulin 58 g/l The bone marrow showed 50% somewhat immature plasma cells She gradually de veloped osteoporosis with compression fractures of the spine and anaemia palliated with transfusions She did not respond to treatment with cyclophosphamide vincris tine and prednisone given between Aug 1977 and April 1978 or to vincristine cyclophosphamide BCNU melpha lan and prednisone administered from April until Sept 1978 when she died

MATERIALS AND METHODS

Light microscopy Films from bone marrow aspirate were fixed in absolute methanol and stained by May-Grun wald-Giemsa at pH 6 8

Electron microscopy The bone marrow aspirate was fixed in 2 5% glutar aldehyde in 0 1 M phosphate buffer pH 7 2-7 4 for 2 hours and postfixed in 1% osmium tetroxide in Tyrode solution pH 7 4 for 1 hour Dehydra tion was carried out in graded ethanols and the specimen was embedded in Epon 812 The sections were cut with an



Fig 2 (a) Plasi one nucleolus a several concent bodies and sin loops" one of t central structur *the smooth end* reticulum of the apparatus (b) D showing the cen *resembling the s* endoplasmic ret Golgi apparatus



LKB Ultramicrotome stained with lead citrate and uranyl acetate and examined in a Siemens El mikroskop 1 electron microscope

RESULTS

Light microscopy On Jan 31 1978 the sternal marrow aspirate was of average cellularity There were about 50% plasma cells with nucleoli and appearing moderately immature The cytoplasm was basophilic In some of the plasma cells the cytoplasm contained a few vacuoles and some irregularities but perhaps not more than usually seen myeloma (Fig 1a colour plate)

Electron microscopy An aspirate fror nal marrow was taken on Jan 31 1978 T cells appeared immature with prominer (Figs 2a and 3a) The RER was well dev about 25% of the plasma cells there was mal pattern of the RER with multiple c lamellar bodies as well as bulging of the tened sac appearing as single sac loops and 3) In the centre of some of the lamellar bodies or single sac loops th 3–15 vesicles of rough endoplasmic reticu 3) In other centres there were structure bling the smooth endoplasmic reticulum of apparatus (Fig 2) The ordinary Golgi these cells was somewhat scanty No s could be seen in some of the centres (Figs 3a)

DISCUSSION

Concentric lamellar bodies derived from plasmic reticulum have previously been some normal cells and in a variety of pathol altered cells (2) probably most often in liver viral hepatitis hepatomas and after adm n of various chemicals to animals Concentric





3 (a) Plasma cell w th *two nucleoli* and several gle sac loops and concentric lamellar bod es at least of them w h 3–15 ves cles of RER n the cent es (*b*) l show ng a centre w th some 15 ve cles of RER

lar bod es re occas nally found n plasma cells (3 4) A port on of cytoplasm conta n ng some organel les particularly l p d droplets and mitochondria (?) l es often sequestered at the centre of such bod es

The RER of our pat ent conta ns mult ple concen tric lamellar bod es *but also in many places a single* flattened sac sect oned in a way resembling a loop sometimes jo ned to another s m lar loop These loops will correspond to a localized bulg ng of the still flattened sac (s ngle sac loops) this bulg ng be ng qu te different from the d stent on of the sacs seen n flam ng plasma cells or from Russel bod es

In some of the centres of the concentric lamellar bod es of s ngle sac loops there are either a number of ves cles of RER (F g 3*b*) or structure resembling the smooth endoplasm c ret culum of *the Golgi apparatus (F g ?b) Th s in add tion to a* somewhat scanty norm l Golgi apparatus m ght suggest a complete rearrangement of the arch tec ture n these cells In other centres there are no central tructures and the bulg ng of the sac m ght then be due to pathology n the all of the sa or in ts format on

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REFERENCES

1 Bessis M Living blood cells and their ultrastructure pp 639–640 Springer Berlin 1973
2 Ghadially F N Ultrastructural pathology of the pp 266–270 Butterworths London 1975
3 Maldonado J Brown A L Bayrd E D & P. G L Ultrastructure of the myeloma cell Ca 19 1613–1627 1966
4 Tanaka Y & Goodman J R Electron microsc human blood cells Harper & Row New York 19

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Multifocal Idiopathic Fibrosclerosis

Two Cases with Simultaneous Occurrence of Retroperitoneal Fibrosis and Riedel's Thyroiditis

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TRACT The concomitant occurrence of ret ritoneal fibrosis (RF) and Riedel s thyroiditis is rted in two patients one of whom presented with ıa The etiology is discussed and it is concluded immunological mechanisms with arteritis might f importance The associations between Riedel s oiditis, RF, mediastinal fibrosis slcerosing chol tis retroorbital fibrosis and fibrosis in other n systems are thought to be different manifesta of a so-called multifocal idiopathic fibro- osis The benefical effect of glucocorticoids in stages of the disease is mentioned

words Riedel s thyroiditis retropentoneal fibrosis *focal idiopathic fibrosclerosis*

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opentoneal fibrosis (RF) and Riedel s thy tis are both rare diseases with aggressive fi is accompanied by infiltrates of inflammatory in the retroperitoneal space and the thyroid d respectively RF as a nosological entity was described in 1948 by Ormond (19) Until now it 500 cases have been published (11) In Scan via the first case was published in 1956 (18) In original paper Riedel described the invasive ous thyroiditis as eisenharte Struma (22) The y of the disease was emphasized by Woolner l (26) who found only 20 cases in 42 000 oidectomies

he present paper describes the association be n RF and R edel s thyroiditis which has not viously been reported from Scandinavia

CASE REPORTS

I

March 1962 a 44-year-old previously healthy female admitted to the Surgical Department because of pain enlargement of the left thyroid gland with tracheal compression symptoms for about 2 months She had had no previous medication The patient appeared euthyroid with an about hen egg sized very hard enlargement of the left lobe of the thyroid gland The right thyroid gland was normal The basal metabolic rate was normal S-creatinine was 0 9 mg/100 ml (under 1 5 mg/100 ml) Carcinoma was suspected and a thyroidectomy was planned but had to be abandoned as the left lobe was severely infiltrated in the adjacent structures A biopsy was performed instead The postoperative course was uneventful and radiation therapy was given During the following year no further compression of trachea occurred and no increase was observed in the thyroid gland S-creatinine was normal

In Nov 1963 the patient was admitted to the Medical Department because of anemia Hb was 62 % S creatinine 4 0 mg/100 ml The diagnosis was chronic pyelonephritis

Owing to progressive nephropathy the patient was readmitted to the Medical Department in Sept 1965 Her S-creatinine at that time was 11 4 mg/100 ml A retrograde pyelography revealed hydronephrosis on both sides with obstruction and medial displacement of both ureters at the fourth lumbal level At this time the patient felt well and as the S-creatinine decreased to 8 5 mg/100 ml during 1½ months in the hospital no further investigation was car ried out

In Sept 1967 the patient was referred to the Medical Department on account of lassitude giddiness and pol lakisuria A right sided pyelography revealed unchanged hydronephrosis and S-creatinine was 8 5 mg/100 ml No proteinuria was found RF was suspected and radiation therapy was given Three months later the patient s S creatinine was 9 8 mg/100 ml She was transferred to Aarhus Kommunehospital where a laparotomy revealed that both ureters were encased in a hard fibrous mass from the level of the promontory and 6 cm distally Ureterolysis was performed on both sides but S-creatinine remained unchanged in spite of normal diuresis The patient de teriorated slowly and died about 9 months later

Further laboratory studies From the first admission onwards the patient had elevated ESR ranging from 44 mm/h to 105 mm/h The thyroid parameters were normal during the whole period No elevation of thyroid globulin antibodies was found and no abnormality in serum protein electrophoresis was detected

Pathology Microscopic examination of the thyroid biopsy showed severe atrophy of the thyroid follicles with interstitial fibrosis and infiltration with lymphocytes plasma cells and scattered eosinophils No signs of malig



Fig 1 Case 1 The thyro d gland with severe fibros s with out remnants of foll cles (H & E)

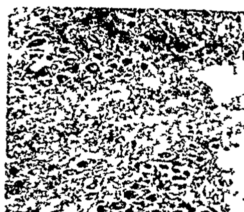


Fig 2 Case 1 Perithyro d t ssue with severe f spl tting of the striated muscle fbres There s lymphocyte nfltrat on (H & E)

nancy were found Some small arteries showed int mal th cken ng and infltrat on of the wall w th lymphocytes The conclusion was Riedel s thyro d tis (Figs 1 3)

Post mortem examination revealed a very hard fbrous mass in the retroperitoneal space extend ng from the promontory to the pelv s and obstruct ng both ureters Hydronephrosis was found on both s des The left thyroid gland had shrunk to a hard fibrous mass The right thyro d gland was normal M croscop c exam nat on of the thyroid glands revealed severe interst t al fbrosis of the left gland compat ble w th R edel s thyroid tis The ret roperitoneal tissue was not exam ned microscop cally There was no s gn of fbrosis in the other organ systems

Case 2

A 62 year old previously healthy female was adm tted to the Surg cal Department in Dec 1976 because of pa nless enlargement of the left thyro d gland w th tracheal com pression symptoms which had lasted for about 6 weeks She had taken no med c ne prior to the occurrence of the thyro d swell ng The patient appeared euthyroid with a very hard nodular enlargement of the left lobe of the thyro d gland All thyro d parameters were within normal limits In order to exclude the poss b lity of carcinoma a subtotal thyroidectomy was performed The left lobe was stone hard and mal gnancy was suspected No inf ltra t on of the adjacent structures was found A nodular go ter was seen on the right s de The postoperat ve course was uneventful but 2 months later the pat ent developed hypo-thyro d sm which was treated with supplementary medi cation

In April 1977 the pat ent was referred to the hosp tal because of recurrence of the tumor in the left thyroid gland Th s t me only a b opsy was performed to exclude mal gnancy defin tely

In Nov 1978 the patient was adm tted to the Medical Department due to lethargy anorexia edema in the lower extrem t es and face and a weight gain of 8 kg last ng for a fortn ght S creat n ne was markedly elevated (7 1 mg/100 ml) No proteinuria was found Hydronephros s w th di lated ureters on both s des was seen on an i v pyelo-graphy and a retrograde pyelography revealed hydronephros s was due to obstruct on in the l of the ureters The left k dney was shrunken (F

The pat ent was transferred to the Urolog ca ment Aarhus Kommunehosp tal where a surgi rat on revealed RF surround ng the common il a at the fourth and fifth lumbal level and obstruc ureters Ureterolys s was done on both s des an ters were placed ntraperitoneally Postoperative t ent developed deep venous thrombos s in the The k dney funct on became normal by the 1 operative day

Further labor tory st l es Ever since the f s on the pat ent had had an elevated ESR rang n to 74 mm/h Serum protein electrophores s wa before the last operat on but postoperatively l munoglobul nem a was found with elevated l that t me the following laboratory tests were antinuclear factor LE cell factor rheumatoid Rose Waaler s test and ant streptolyc n C 3 co was slightly below the normal l m t

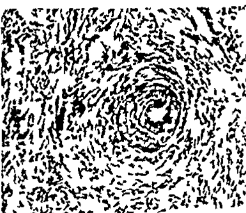


Fig 3 Case 1 The fbrotic thyro d gland contains arteries with lymphocytic infltrat on and th kening walls (H & E)



F g 4 Case ? Retrograde pyelography show ng med al dev at on and constrict on of the lower th rd of the ureters w th hydroureter and hydronephros s

holog M croscop c exam nat on of the thyro d ?l from the f rst as well as the second thyro d operat on ?ed severe chron c and subchron c inflammatory nges w th lymphocytes plasma cells and scattered noph ls A mass ve f b os s was found The patholog nd ngs extended throughout the thyro d capsule into acent musculature and ad pose t ssue No s gns of ulomatous react on were seen (F g 5)

nat on of a k dney b opsy taken prior to the op- on revealed sl ght nterstit al f bros s On mmuno- rescence m croscopy and electron m croscopy no lar or vacuolar depos t ons were seen M cro- c exam nat on of the retroperitoneal t ssue showed ns ve f bros s w th sparse remnants of fat cells There m ld mononuclear cell nfiltrat on wh ch was patch ly ed Small arteries show thicken ng of the walls no arterit s (F g 6)

DISCUSSION

Retroperitoneal fibrosis is characterized by a chron c inflammatory and prol ferat ve f brous process with various degrees of cellular infiltrat on of lymphocytes plasma cells neutroph l c cells and eos noph ls occurring in the loose areolar connec t ve and adipose tissue just beneath the posterior parietal peritoneum of the abdomen and pelvis (8) The ureters are the retroperitoneal structures most frequently involved (11) but cases have been re ported in wh ch obstruct on of the great vessels the b l ary tracts the duodenum the retros gmo deum and mesenterial vessels have occurred (11) The symptoms and the pathology of RF have been d s



Fig 5 Case 2 Thyroid gland with severe fibrosis and disappearance of all follicles (H & E)



Fig 6 Case 2 Retroperitoneal fat tissue with fibrosis and patchy lymphocytic infiltration (H & E)

cussed previously (7) The etiology of RF remains an enigma Koep and Zuidema (11) found an association with methysergide in 12 4% of their cases Several other etiological factors have been mentioned such as malignancies phlebitis in the pelvic veins retroperitoneal hematoma aortic aneurysm chronic intestinal inflammation sarcoidosis obstructive lymphangitis adipose tissue inflammation (Weber Christian) leakage of urine toxoplasmosis (11 16) and α methyldopa (6)

The pathological changes resemble those seen in collagen diseases and consequently immunological mechanisms have been considered (8) A few cases have been reported in which RF has been associated with lupus erythematosus vasculitis (17) amyloidosis (13 21) immune complex glomerulonephritis (10) Raynaud s phenomenon (17) HLA B 27 antigen (25) as well as deposits of IgG IgA IgM on the collagen fibres (6) It has been postulated that methysergide and other drugs act as haptens (8) The good response to steroids in the early stages of RF might support the theory of an immunological hypersensitivity reaction (17)

Riedel s thyroiditis is a unilateral or bilateral proliferative fibrosis which not only involves the thyroid gland but also extends throughout the thyroid capsule into the adjacent structures of the neck and is accompanied by infiltrates of inflammatory cells without giant cells lymph follicles and granuloma causing destruction of the thyroid parenchyma (26) There are no characteristic biochemical findings associated with the disease The thyroid function is usually normal and no thyroid antibodies can be demonstrated Yet the ESR is generally raised (24) Palpation can[not dif]ferentiate Riedel s thyroiditis from carcinoma [of the] thyroid gland The etiology is obscure The [previ]ous view, that Riedel s thyroiditis is a late s[tage of] either Hashimoto s or de Quervain s thyroidi[tis has] now been abandoned (24)

Barrett (2) observed that the pathological c[hanges] in Riedel s thyroiditis RF pseudotumor of [the or]bit and mediastinal fibrosis are akin to each [other]. Tubbs (23) published in 1946 a case with co[ncomi]tant occurrence of mediastinal fibrosis and [RF. In] recent years several cases with simultaneo[us oc]currence of sclerosing fibrosis in a number of [wide]ly separate organ systems have been descri[bed (1] 3 11 12 16 20) The combination of R[F and] Riedel s thyroiditis has been reported in on[ly . . .] cases (3 4 9 11 14 15 16)

It has been suggested that these apparently [sepa]rate fibrotic lesions may be different manifest[ations] of the same disease called multifocal or sy[stem]ic idiopathic fibrosclerosis (16) Immunol[ogical] mechanisms are thought to be etiologically i[mpor]tant (9) and it is interesting that Hardmeie[r and] Hedinger (5) found vascular inflamma[tion in] Riedel s thyroiditis similar to Takayasu s arte[ritis]. Familial occurrence has been reported (1) a[nd a] case with α 1 antitrypsin deficiency has been [pub]lished (20) In the present cases arteritis was f[ound] in the thyroiditis of case 1 but no biochemical s[igns] of systemic collagen disease were detected

The treatment of multifocal idiopathic f[ibro]sclerosis is controversial All medication sh[ould] be discontinued Surgical intervention is neces[sary] when obstruction occurs Administration of

osteroids has given only equivocal results but ght be more beneficial in the early stages of the ease (9 17)

REFERENCES

1 Amoroso L F Shear M K & Spiera H Multifocal fibrosis involving the thyroid face and orbits Arch Intern Med 136 221 1976

Barrett N R Idiopathic mediastinal fibrosis Br J Surg 46 207 1958

Comings D E Skubi K B van Eyes J & Motulsky A G Familial multifocal fibrosclerosis Ann Intern Med 66 884 1967

Gleeson M H Taylor S & Dowling R H Multifocal fibrosclerosis Proc R Soc Med 63 43 1970

Hardmeier Th & Hedinger Chr Die eisenharte Struma Riedel—eine primare Gefasserkrankung Virchows Arch (Pathol Anat) 337 547 1964

Iversen B M Nordahl E Thunold S Johannessen J W Ofstad J & Willassen Y Retroperitoneal fibrosis during treatment with methyldopa Lancet 302 1975

Jensen O Møller Retroperitoneal fibrose Ugeskr Laeger 134 1327 1972

Jones J H Ross E J Matz L R Edwards D & Davies D R Retroperitoneal fibrosis Am J Med 8 203 1970

Katsikas D Shorthouse A J & Taylor S Riedel s thyroiditis Br J Surg 63 929 1976

Katz S M Bates O Yudis M Falkner B & Griffith E Immune complex glomerulonephritis in case of retroperitoneal fibrosis Am J Clin Pathol 67 436 1977

Koep L & Zuidema G D The clinical significance of retroperitoneal fibrosis Surgery 81 250 1977

Jensen A & Lindeneg O Idiopatisk retroperitoneal og mediastinal fibrose Nord Med 79 678 1968

13 Littman E Renal amyloidosis with nephrotic syndrome associated with retroperitoneal fibrosis Ann Intern Med 74 240 1971

14 Meijer S Hoitsma H F W & Scholtmeijer R Idiopathic retroperitoneal fibrosis in multifocal fibrosclerosis Eur Urol 2 258 1976

15 Meyer S & Hausman R Occlusive phlebitis in multifocal fibrosclerosis Am J Clin Pathol 65 274 1976

16 Mitchinson M J The pathology of idiopathic retroperitoneal fibrosis J Clin Pathol 23 681 1970

17 Morandi L P & Grob P J Retroperitoneal fibrosis Arch Intern Med 128 295 1971

18 Nannestad J Stenosis ureteris bilateralis Ugeskr Laeger 118 605 1956

19 Ormond J K Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process J Urol 59 1072 1948

20 Palmer P E Wolfe H J & Kostas C I Multisystem fibrosis in alpha 1 antitrypsin deficiency Lancet 1 221 1978

21 Pugh R C B The pathology of fibrotic lesion Proc R Soc Med 53 685 1960

22 Riedel B M K L Die chronische zur Bildung eisenharter Tumoren führende Entzundung der Schilddruse Verh Dtsch Ges Chir 25 101 1896

23 Tubbs O S Superior vena caval obstruction due to chronic mediastinitis Thorax 1 247 1946

24 Volpe R Fibrous (Riedel s) thyroiditis In The thyroid 4th ed (ed S C Werner & S H Ingbar) pp 1009–1012 Harper & Row Hagerstown 1978

25 Willscher M K Novicki D E & Cwazka W F Association of HLA B 27 antigen with retroperitoneal fibrosis J Urol 120 631 1978

26 Woolner L B McConahey W M & Beahrs O H Invasive fibrous thyroiditis (Riedel s struma) J Clin Endocrinol Metab 17 201 1957

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Cortisone-Induced Remission of Hypothyroidism in Schmidt's Syndrome

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STRACT A patient with autoimmune Addison s ease hypothyroidism and primary gonadal insuf ency is described Initial treatment with cortisone roved his thyroid function, probably through cor ne suppression of the autoimmune reactions It however, not possible to normalize the thyroid ction completely The decreased testicular func i did not improve during the cortisone treatment

words Schmidt s syndrome cortisone induced re ion

i Med Scand 208 125 1980

association between Addison s disease and var endocrine disorders has been established since midt (14) described two patients with non rculous Addison s disease and chronic lym cytic thyroiditis proved at autopsy Since then eral investigators (1 2 6 8 10 15) have de bed an increased incidence of diabetes mellitus roid disorders pernicious anaemia idiopathic oparathyroidism and primary hypogonadism in ents with idiopathic Addison s disease Occur e of organ specific antibodies is a characteristic hese disorders

1 the following we describe a patient with mul docrine insufficiency of autoimmune origin in om the hypothyroidism remitted during cor ne replacement therapy

CASE REPORT

ale born in 1947 without any family history of endo- e disorders At the age of 17 he became slightly gued Several times he consulted a general practitioner in Oct 1974 found a decreased S thyroxine value of nmol/l (normal level >61) No treatment was instituted he spring of 1975 the patient went for a holiday to lta where he was admitted to a hospital because of sea vomiting and abdominal pain Apart from i v id he received no treatment After his return he was admitted to our hospital On admission he felt completely well

At examination pigmentation of oral mucosa was pres ent Apart from this the physical examination gave nor mal results Blood pressure was 110/80 mmHg S sodium 120–128 mEq/l S potassium 5 7–4 8 mEq/l 24 hour excretion of 17 KGS 1 0–1 6 mg (normal range 6 7–19 2) No significant increment following stimulation with 1 mg Synacthen® i m daily for 3 days Plasma cortisol was less than 110 nmol/l (normal range 240–830) No increment of plasma cortisol was registered after stimulation with 0 25 mg Synacthen® given as a single i m injection After stimulation with 1 mg Synacthen® daily for 3 days plasma cortisol increased to subnormal values (116 and 154 nmol/l) TSH was 340 mU/l (normal range <1 9) Total S thyroxine was 19 nmol/l (normal range 60–140) T_3 RIA was 1 21 nmol/l (normal range 1 14–2 30) LH was within the normal range at repeated examinations FSH was con stantly increased 31 35 and 32 mU/ml (normal range 5–20) S testosterone was 472–733 μg/100 ml (normal range 298–791) I v glucose tolerance test including insulin measurements was within the normal range Organ specific antibodies see Table I X rays of sella turcica thorax and adrenals (including tomography) were normal Ophthalmoscopy and vision field were normal Histocom patibility (HLA) antigen type was HLA A 1 29 B 8 4 A 2 (TT)

The patient was treated initially with cortisone acetate and later with fludrocortisone acetate as shown in Fig 1 The clinical remission was immediate and impressive S sodium and S potassium normalized quickly The course of the thyroid function tests is shown in Fig 1 In Jan 1976 the patient felt increasing fatigue but had no other complaints The dose of cortisone was increased but as this had no effect on the patient s condition and as the thyroid function was not within the normal range therapy with levothyroxine was started The patient has since then been in clinical remission The patient a single man has on no occasion made any spontaneous complaints about his sexual function

DISCUSSION

The examinations demonstrate that the patient suf fers from both hypothyroidism and Addison s dis ease (Schmidt s syndrome) The increased FSH

Table I *Organ specific autoantibodies before and after initiation of cortisone replacement therapy*

	Before treat ment	After treat ment
Thyroglobulin antibody CA 1	0	0
Second colloid antibody CA 2	+	0
Microsomal thyroid antibody	+	+ ++
Adrenocortical antibody		+
Parietal cell antibody		0
Islet cell antibody		0

values indicate that he also has insufficient gonadal function (7 9)

Idiopathic Addison s disease is considered an autoimmune disorder with occurrence of antibodies against the adrenal cortex (1, 5, 6 11) in contrast to tuberculous hypocorticism (5 11)

Primary hypothyroidism is likewise considered an autoimmune disease possibly the final stage in Hashimoto s thyroiditis (4 12) The autoimmune pathogenesis for two of the patient s endocrine diseases suggests that the same mechanism may be responsible for the third the insufficient gonadal function

The patient s thyroid function improved after the start of cortisone replacement therapy The TSH values decreased significantly and S thyroxine increased to subnormal level Significant and lasting improvement of thyroid function in four patients with Schmidt s syndrome substituted solely with adrenal steroids has previously been described (3) It has been suggested that the underlying mechanism is a suppression of the destructive process in the thyroid gland by adrenal steroids Adrenal steroids exert an effect on the pituitary function Re et al (13) have demonstrated that glucocorticoids in physiological and pharmacological doses suppress the S TSH level in euthyroid and hypothyroid subjects through an effect on the pituitary gland and that S thyroxine is not altered by the glucocorticoids The significant and lasting decrease in S TSH and the synchronous increase in S thyroxine in our patient clearly cannot be ascribed to a glucocorticoid effect on the pituitary gland but indicate that a regeneration of the thyroid function has taken place

Gharib et al (3) assume that the restitution of the thyroid function is due to a suppressing effect of cortisone on the destructive processes in the thyroid gland In our patient the CA 2 antibodies

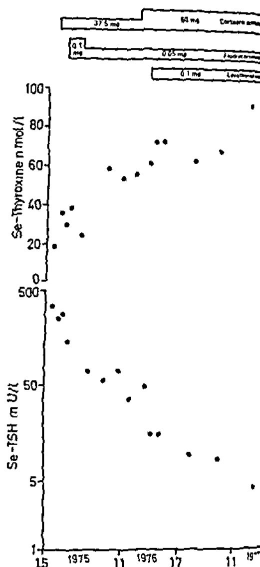


Fig 1 Total S thyroxine (normal range 60-140 n... and S TSH (normal level ~1 9 mU/l) plotted against...

disappeared synchronously with the improv... of the thyroid function This might suppor... hypothesis that cortisone in physiological d... suppresses the immunological processes resp... ble for the impaired thyroid function It is h... ever remarkable that the other autoantibod... not changed in our patient and that the testi... dysfunction was not improved

REFERENCES

1 Carpenter C C J Solomon N Silverberg S Bledsoe T Northcutt R C Klinenberg J Bennet J L Jr & Harvey A M Medicine (Baltimore) 43 153 1964

Gharib H & Gastineau C F Mayo Clin Proc 44 217 1969
Gharib H Gastineau C F Hodgson S F Scholz D A & Smith L A Lancet 2 734 1972
Goudie R B Anderson J R Gray K G Clark D H Murray I P C & McNicol G P Lancet 2 976 1957
Irvine W J Proc R Soc Med 61 271 1968
Irvine W J & Barnes E W Clin Endocrinol Metabol I 549 1972
Kjessler B & Wide L Acta Endocrinol (Kbh) 72 ̲43 1973
Maisey M N & Lessof M H Br Med J III 392 1969
9 Mauss J & Borsch G Acta Endocrinol (Kbh) 74 631 1973
10 Nerup J Addisons disease Thesis Copenhagen 1974
11 Nerup J Søborg M Halberg P & Brøchner Mortensen K Acta Med Scand (Suppl) 445 383 1966
12 Owen S G & Smart G A Lancet 2 1034 1958
13 Re R N Kourides I A Ridgway E C Weintraub B D & Maloof F J Clin Endocrinol Metab 43 338 1976
14 Schmidt M B Verh Dtsch Ges Pathol 21 212 1926
15 Turkington R W & Lebovitz H E Am J Med 43 499 1967

Symptomatic Diabetes Mellitus Cured by Potassium and Withdrawal of Polythiazide in a Hypokalemic Hypertensive Woman

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STRACT A case of symptomatic diabetes mel s in a 65 year old woman with 14 years of ythiazide treatment and hypokalemia is described condition was cured by potassium administration l withdrawal of the thiazide diuretic

words diabetes mellitus diuretics potassium de ncy

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rioration of glucose tolerance caused by zide diuretics and probably mediated by hy *alemia has been observed for several years* 6 9 11 12 13 14 18 19 20) Most often this rioration is moderate The present case history y therefore be of some interest as it concerns a id symptomatic case of diabetes mellitus cured withdrawal of polythiazide and administration of assium in a hypokalemic hypertensive patient

CASE HISTORY

5 year-old woman was admitted to hospital because of etes She had no family history of diabetes or hyper ion Cholecystectomy at age 44 Hysterectomy for oma uteri at age 50 Subtotal thyroidectomy for toxic use goiter at age 51 When she was 52 years old a ral practitioner detected arterial hypertension The erical values of blood pressure at that examination are available The patient had never suffered from dys a chest pain or swollen legs Polythiazide (Renese®) g once a day was prescribed One month before admis to our hospital she noticed thirst and frequent urina s with large amounts of urine Diabetes mellitus was overed and the patient was hospitalized
t bedside examination she was dehydrated There was dyspnea cyanosis or signs of abnormal thyroid func The cardiac and pulmonary auscultatory findings e normal The blood pressure was 165/95 mmHg body ght 74 5 kg Hb 168 g/l ESR 4 mm/h ECG showed a complex in leads V_1–V_3 indicating transmural anterior damage of the myocardium of unknown age Furthermore distinct U waves were found The fasting blood sugar was 24 5 mmol/l and 258 mmol glucose was excreted during 24 hours in 2 l urine Trace amounts of ketone bodies were found in the urine Serum concentration of sodium was 142 potassium 2 6 and chloride 94 mmol/l indicating grave alkalotic hypokalemia Serum creatinine was 71 mmol/l Albustix® was negative

In view of the possible connection between thiazide in duced hypokalemia and diabetes mellitus treatment was started with seponation of polythiazide and oral adminis tration of 4 g potassium chloride b i d Diabetes diet was prescribed during five days whereafter the patient was transferred to an ordinary diet The fasting blood glucose level progressively fell during a period of 12 days after which it was 5 8 mmol/l (Fig 1) Normal value in this age group is 4 6±0 5 mmol/l (mean ± S D) The glucosuria gradually disappeared and could not be demonstrated af ter the seventh hospital day Trace amounts of ketone bodies initially found in urine had disappeared after two days The body weight increased from 74 5 to 76 2 kg during the first two weeks in hospital Serum potassium rose to 3 9 and serum chloride to 106 mmol/l during the same period

After two weeks the patient felt quite well and left the hospital with potassium chloride 1 g t i d as the only prescription Two months later she felt well and had no symptoms of diabetes mellitus The fasting serum glucose level was then 4 9 mmol/l which is within the normal range The peroral glucose tolerance test showed a maximum of 10 7 mmol/l 60 min after administration of 1 g glucose/kg b wt a value also within the normal limits Serum sodium was 141 potassium 4 0 and chloride 106 mmol/l She weighed 75 kg and had a blood pressure of 150/90 mmHg The patient had a slight angina pectoris and nitroglycerin was prescribed Otherwise she had no drug or diet therapy

DISCUSSION

Both well controlled diabetes patients and patients without prior evidence of carbohydrate intolerance have developed hyperglycemia and glucosuria after



Fig 1 Serum potassium (—) blood glucose (—) after polyth[illegible] drawal and institution of tre[illegible] potassium chloride 1 g t i d

treatment with thiazide diuretics for periods varying from one day to several years (2 6 9 11–14 18–20) The topic has been extensively reviewed by Bengtsson (2) who also found contradictory reports in the literature In particular longer acting thiazide diuretics like polythiazide have been reported to give an adverse effect on glucose tolerance (5) Previous evidence of this adverse thiazide effect has been casuistic or founded on patient series without randomized controlled trails so that it has been difficult to differentiate between spontaneous and drug induced changes in glucose metabolism A reversibility of the impairment of carbohydrate tolerance on seponation of diuretics has suggested drug effects in some cases (2 12) Recently Amery et al (1) have strengthened the concept of an adverse effect of thiazide diuretics on carbohydrate tolerance in a double blind randomized controlled trial of 119 elderly hypertensive patients These authors found that unlike the findings in a placebo group the average fasting blood sugar rose and the glucose tolerance during an oral glucose load deteriorated progessively at controls 1 2 and 3 years after treatment with 25 mg hydrochlorothiazide and 50 mg triamterene During the three years the average rise in fasting blood sugar was 14 mg/100 ml (1 mmol/l) The changes in glucose tolerance in this series must be characterized as mild and no cases of diabetes developed The deterioration in glucose tolerance did not appear to be limited to a few patients but occurred across the board" This suggests that the risk of inducing clinical diabetes by means of thiazide treatment is largest in persons with borderline diabetes It is therefore important to observe that hypertension which is a main indication for thiazide therapy is associated with diabetes irrespective of [illegible] tensive treatment (7)

The mechanism behind the effect of t[illegible] glucose tolerance is not entirely clear b[illegible] lines of evidence point to a close conn[illegible] tween thiazide induced potassium loss [illegible] paired glucose tolerance It has been kn[illegible] long time that the potassium ion influe[illegible] bohydrate metabolism in several ways fo[illegible] as an activator of enzymatic reaction[illegible] glucogen formation (10) Sagild et al (17) [illegible] marked decrease in carbohydrate tolera[illegible] potassium depletion was induced in norm[illegible] oral ion-exchange resin This finding is [illegible] harmony with results of potassium depleti[illegible] (8) as well as with the observation of Rap[illegible] Hurd (16) that glucose tolerance improv[illegible] potassium supplementation in thiazide tr[illegible] tients with hypokalemia The same effect [illegible] sium supplementation has been observed i[illegible] who are hypokalemic from primary or s[illegible] hyperaldosteronism (15) The study by Am[illegible] (1) also demonstrated a close parallelism [illegible] the lowering of serum potassium and dete[illegible] of carbohydrate tolerance On the other ha[illegible] studies have failed to demonstrate any ass[illegible] between hypokalemia and pathological gl[illegible] erance during treatment with thiazide d[illegible] 14)

The patient presented here shows a su[illegible] versibility of symptomatic diabetes associ[illegible] thiazide treatment and hypokalemia This s[illegible] that withdrawal of thiazide diuretic in co[illegible] with correction of potassium deficiency occ[illegible] ly may cure symptomatic diabetes mell[illegible] previously known that potassium supple[illegible]

well as withdrawal of th az de d uretics may im ve glucose tolerance in both diabetic and non bet c subjects (13 15 16) but the present patient ms to be remarkable in view of the high degree mprovement In a survey of the literature I nd only one report with a comparable improve nt of d abetes on w thdrawal of d uretic treat nt (1?) and that report conta ned no data on ım potassium levels

REFERENCES

Amery A Berthau P Bulp t T C Deruytere M de Schaepdryver A Dolery C Fagard R Foret te F Hellemans J Lund Johansen P Mutses A & Tuom leh o J Glucose ntolerance during d uret c herapy Lancet 1 681 1978

Bengtsson C Impa rment of glucose metabol sm during treatment w th ant hypertens ve drugs Acta Med Scand (Suppl) 6?8 63 1979

G Andersson O Larsson O & W l helmsson L Ant hypertensive effect and s de-ef ects of bendrofl methiaz de and propranolol Acta Med Scand 199 499 1976

Berglund G Larsson B Andersson O Larsson O Svardsudd K Bjorntorp P & W lhelmsen L ody compos t on and glucose metabol sm n hyper ns ve m ddle aged males Acta Med Scand 200 163 976

lery C T D abetogen c effect of long term d u ret c therapy In Modern d uret c therapy n the treat ment of card ovascular and renal d sease (ed E Lant nd L W lson) p 3?0 Excerpta Med ca Amsterdam 973

Dollery C T & Ferguson M J Saluret c drugs and d abetes mell tus Am J Card ol 7 568 1961

du Florey C V Uppal S & Lowy C Hyper glycaem a a risk factor for hypertens on? Rev Ep dem ol Sante Publ ?4 313 1976

8 Gardner L I Talbot N B Cook C D Berman H & Unbe C Effect of potassium def c ency on carbohydrate metabol sm J Lab Cl n Med 36 59? 1950

9 Goldner M G Zarow tz H & Akgun S Hy perglycem a and glucosuria due to th az de deriva tives adm n stered n diabetes mell tus N Engl J Med ?6? 403 1960

10 Hast ngs A B & Buchan J M Role of intracellular cat on on liver glucogen format on n v tro Proc Natl Acad Sc USA 8 478 194?

11 Holl s W C Aggravat on of d abetes during treat ment w th chlorothiaz de JAMA 176 947 1961

12 Jones I G D abetes mell tus follow ng oral d u ret cs Practit oner 199 ?09 1967

13 Kolmer D M Dollery C T Lowy C & Schone B Effect of d uret c therapy on glucose tolerance n hypertens ve pat ents Lancet 1 986 1961

14 Lew s P J Petric A Kohner E M & Dollery C T Deterıorat on of glucose tolerance n hypertens ve pat ents on prolonged d uret c treatment Lancet 1 ?64 1976

15 McFarland K F & Carr A A Changes in the fast ng blood sugar after hydrochloroth az de and potass um supplementat on J Cl n Pharmacol 17 13 1977

16 Rapoport I & Hurd H F Th az de nduced glucose intolerance treated w th potass um Arch Intern Med 113 405 1964

17 Sag ld U V Andersen P & Andreassen P Glu cose tolerance and insul n response n experimental potass um depletion Acta Med Scand 169 ?43 1961

18 Sugar S J N D abetes ac dos s during chloro az de therapy JAMA 175 618 1961

19 W lk ns R W New drugs for treatment of d abetes mell tus Ann Intern Med 50 1 1959

?0 Zatuchn J & Kordasz F The d abetogen c effect of thiaz de d uret cs Am J Card ol 7 565 1961

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A Case of Hypocalcemia, Heart Failure and Exceptional Repolarization Disturbances

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TRACT Little attention has been given to the ion whether clinical heart failure can be a mani ion of hypocalcemia A patient with hypopara idism and heart failure prompted us to analyse ports on this subject The conclusion was that ociated with an underlying myocardial disease calcemia may be a rare contributing factor to failure Hypocalcemic heart failure without ting heart disease has been suggested as a cause potension In two special situations in which a n fall of serum ionized calcium is induced ve transfusions of citrated blood and rapid tion of uremic acidosis In addition to hypocal and heart failure, our patient had exceptional arization disturbances rate-dependent varia of T wave amplitudes during sinus arrhythmia unexpected prolongations of the Q–T interval attacks of ventricular tachycardia

ords hypocalcemia heart failure repolarization cular tachycardia

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port a patient who had suffered from severe ated thyrotoxicosis for several months Six s after thyroid resection she was admitted to tal hypocalcemic with pulmonary edema and rculatory shock The clinical signs of heart e were cured by calcium administration The quent course was complicated by repolariza disturbances and arrhythmias

CASE REPORT

8 year-old girl was admitted to hospital in severe toxicosis after having suffered from palpitations and ts for several months On admission a supraventricu chycardia of 180/min was recorded PBI was 15 9 0 ml There was nothing exceptional in her family or ast history An innocent systolic murmur had been 1 at routine medical check up of school children at the age of 14 Chest roentgenogram and ECG (Fig 1 *A*) were normal at that time

She was treated with carbimazole practolol and preoperatively with potassium iodide The preoperative chest roentgenogram and ECG were interpreted as nor mal On reanalysis of the chest roentgenogram the heart was however found to be slightly enlarged (Fig 2*A*)

She underwent an ordinary thyroid resection and was discharged in good condition At home she began to feel progressive muscle twitches and weakness on exertion but did not consult a doctor Six weeks after operation she became powerless and was readmitted

A pale exhausted and dyspneic girl was seen on admis sion Her physique was normal weight 62 kg height 164 cm She was in circulatory shock the arterial pulse was feeble and the blood pressure could not be recorded the skin was cold and clammy Moist rales were heard over both lungs Neck veins were not distended and there was no peripheral edema Chvostek s sign was strongly posi tive ECG displayed sinus tachycardia of 125/min left atrial strain and a markedly prolonged Q–T interval The observed Q–T interval (Q–T) was 0 38 sec the normal Q–T interval (Q–T) for the heart rate being 0 27 sec (Fig 1 *B*) Chest roentgenogram showed alveolar edema and an enlarged heart (Fig 2 *B*) Because of the strong clinical suspicion of postoperative hypoparathyroidism adminis tration of calcium gluconate was started immediately De termined on admission serum calcium 4 8 mg/100 ml and serum phosphate 8 5 mg/100 ml confirmed the clinical diagnosis After i v administration of 20 ml of 10% cal cium gluconate as an emergency treatment blood pres sure rose to 90 mmHg The central venous pressure was 12 cm H O electrolytes were normal During the follow ing 12 hours the patient received a total of 60 ml calcium gluconate as the only treatment (apart from oxygen and i v infusion of 5% glucose with potassium but neither digitalis nor vasopressors or diuretics) She improved re markably the blood pressure rose to 105/90 mmHg and the chest roentgenogram showed clear lung fields Echocardiogram excluded pericardial effusion as the cause of the heart enlargement Oral substitution of cal cium and dihydrotachysterol was instituted

During the following two weeks transient periods of marked sinus arrhythmia developed with rate-dependent

Abbreviations Q–T observed Q T interval Q–T normal Q–T interval

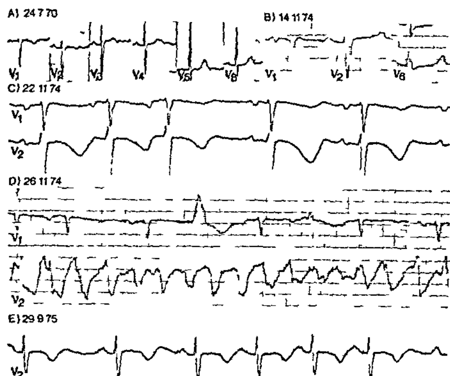


Fig 1 Serial ECG sec) (*A*) Normal f (notched T waves) preoperatively (*B*, longed Q–T interv; atrial strain on adr (*C*) Marked sinus a with rate-depender variation (*D*) S na arrhythmia and late tricular extrasystol V 1) preceding an a ventricular tachyc: V2 chosen to show changing direction complex) (*E*) Sinu mia without T wav tion after recovery

variation of T wave amplitudes and hysteresis of Q–T interval (Fig 1 *C*) Accompanying these periods the patient had recurrent attacks of ventricular tachycardia The ventricular tachycardias were heralded by subjective feeling of hot waves going over the body and bursts of late ventricular extrasystoles apparently provoked by long R–R intervals during sinus arrhythmia (Fig 1 *D*) During intervening normal sinus rhythm unexpected varying prolongations of the Q–T interval were noted ($Q{-}T_o$ up to 50% longer than $Q{-}T_n$) The Q–T interval was most markedly prolonged during days with several episodes of ventricular tachycardia This fluctuation of the Q–T interval did not parallel the level of serum calcium sudden Q–T prolongations occurred during stable normocalcemia No explanation of these disturbances was found at a thorough examination All routine laboratory tests e g serum magnesium and proteins were normal

The patient gave a strong clinical impression of an enhanced sympathetic tone with her apprehensive appearance and dilated pupils but urinary excretion of epinephrine norepinephrine metanephrines and vanillyl mandelic acid as well as electroencephalogram were normal The following drugs proved ineffective lidocaine with or without overdrive ventricular pacing practolol procainamide and quinidine Mostly the tachycardias disappeared spontaneously tens of DC shocks were also needed After starting diphenylhydantoin treatment 300 mg daily the arrhythmias and Q–T prolongations discontinued abruptly and completely and did not recur The patient was discharged in good condition on 2 g calcium 0 4 mg dihydrotachysterol and 300 mg diphenylhydantoin daily

A check up one year later revealed that the heart size had reverted to normal (Fig 2*C*) Signs of autonomic lability were found when the patien from the supine to upright position In the su tion the blood pressure was 146/88 mmHg displayed sinus rate of 63/min Q–T equal to (a normal T wave polarity Standing up caused the blood pressure to 110/90 mmHg and marked changes in the ECG sinus arrhythmia with a r 125/min and hysteresis of Q–T interval inversi waves but no rate-dependent amplitude variatio time and high voltage P waves (Fig 1*E*) T arrhythmia could not be provoked after pretreatm propranolol 5 mg i v

The physical performance of the patient was and she tolerated heart rates of over 180/min on ergometer without subjective symptoms or abno in the ECG

Administration of diphenylhydantoin was d without adverse consequences An attempt was withdraw calcium and dihydrotachysterol but sh not do without substitution When seen three yea she was still feeling completely healthy and had any heart disturbances

DISCUSSION

Though calcium plays a key role in the con process in myocardial cells the clinical sy of hypocalcemia usually derive from an in excitability of the nervous system and h cemia is rarely considered as a cause of hea

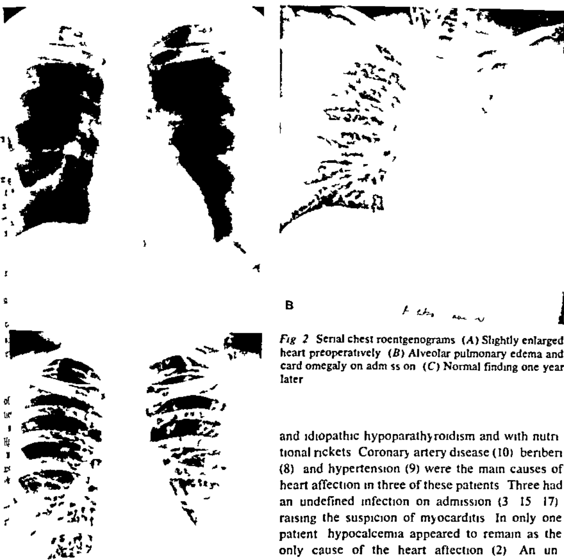


Fig 2 Serial chest roentgenograms (*A*) Slightly enlarged heart preoperatively (*B*) Alveolar pulmonary edema and cardiomegaly on admission (*C*) Normal finding one year later

In neonatal hypocalcemia symptoms have partly attributed to heart failure (7 18) How r the correct interpretation of the clinical signs ifficult since edema in neonatal hypocalcemia is necessarily a sign of heart failure but may re from renal effects of hypocalcemia itself (18)

alcemia causing or aggravating heart failure an apparent response to calcium therapy has n reported in few patients with postoperative and idiopathic hypoparathyroidism and with nutritional rickets Coronary artery disease (10) beriberi (8) and hypertension (9) were the main causes of heart affection in three of these patients Three had an undefined infection on admission (3 15 17) raising the suspicion of myocarditis In only one patient hypocalcemia appeared to remain as the only cause of the heart affection (2) An unexplained symptomless cardiomegaly and return of heart size to normal with restoration of normocalcemia has been reported twice in hypoparathyroidism (1 4)

Heart failure has not been ascribed to hypocalcemia in chronic untreated uremia The explanation might be uremic acidosis keeping the serum level of ionized calcium A rapid fall in ionized calcium during vigorous treatment of advanced uremia (5) as well as massive transfusions of citrated blood (6 20) may lead to hypotension the suggested pathogenesis being a reduction of the systemic resistance and/or decrease in contractile force

In our patient pulmonary edema and circ shock denoting left ventricular failure were s fully treated with calcium alone Even so h

cemia alone could hardly have caused her clinical condition The condition was acquired one year after this episode there were no signs of a heart disease The long and fulminant history of thyrotoxicosis with supraventricular tachycardia of 180/min on the first admission and the radiological evidence of heart enlargement preoperatively suggested that she had an underlying thyrotoxic heart disease This and the previous case histories suggest that if associated with an underlying myocardial disease hypocalcemia may be a rare contributing factor to heart failure However in special situations a sudden fall in ionized calcium may be enough for making the heart fail

The repolarization disturbances and arrhythmias need commenting Normally T wave amplitude is stable during sinus arrhythmia (13) as it was in our patient after recovery (Fig 1 *E*) but during the acute phase the amplitude varied with the length of the preceding diastole (Fig 1 *C*) This phenomenon has been previously described in atrial fibrillation as a sign of heart disease probably resulting from the mechanical effect of varying diastolic filling on repolarization of diseased myocardium (16) During the attacks of ventricular tachycardia the direction of QRS complex undulated (Fig 1 *D*) resembling torsade de pointes an atypical ventricular tachycardia which occurs especially in patients with prolonged Q–T interval due to asynchrony of repolarization (11) However repolarization remains synchronized in hypocalcemia and there should be no predisposition to torsade de pointes Furthermore the ventricular tachycardias and Q–T prolongations were unrelated to the serum calcium level Several features of our patient (sudden prolongations of Q–T interval feeling of hot waves preceding the ventricular tachycardias periods of sinus arrhythmia) were typical of the hereditary Romano-Ward syndrome (12 19) in which changes in autonomic tone with inappropriate cardiac sympathetic discharges are supposed to induce asynchronous repolarization and precipitate ventricular arrhythmias Suggestively our patient exhibited signs of a marked constitutional autonomic lability already reflected by the notched T waves (14) in her childhood ECG (Fig 1 *A*) The effects of this autonomic lability on diseased myocardium could have been of significance

REFERENCES

1 Antebi L Bouchard R Guedeney J Perl Weill J Cardiomegaly due to chronic hypoc Pediatrics 38 909 1966
2 Aryanpur I Farhoudi A & Zangeneh F tive heart failure secondary to idiopathi parathyroidism Am J Dis Child 127 738 19
3 Brenton D P Gonzales J & Pollard Hypocalcemic cardiac failure Postgrad M 633 1978
4 Bronsky D Dubin A Waldstein S S & D S Calcium and the electrocardiogram. trocardiographic manifestations of hypo roidism. Am J Cardiol 7 823 1961
5 Chaimovitz C Abinader E Benderly A O S Hypocalcemic hypotension JAMA 1972
6 Denlinger J K & Nahrwold M L Cardia associated with hypocalcemia Anesth Anal 55 34 1976
7 Edge W E B Hypocalcaemia in infancy cial reference to cardiac failure S Afr Med 1963
8 Evans J A & Elliott F D Multiple vit ficiencies including beriberi heart with co failure Lahey Clin Bull 4 173 1945
9 Grieve S & Schamroth L Idiopathi parathyroidism S Afr Med J 29 232 1955
10 Hegglin R Herz und Hypokalzamie Helv 6 584 1939
11 Krikler D M & Curry P V L Torsade d an atypical ventricular tachycardia Br 38 117 1976
12 Mathews E C Blount A W & Townse Q–T prolongation and ventricular arrhythm and without deafness in the same family A diol 29 702 1972
13 Matyas T A T wave amplitude stability sinus arrhythmia in the resting man Physio 16 115 1976
14 Millar K & Abildskov J A Notched T w young persons with central nervous system Circulation 37 597 1968
15 Najjar S S Nassif S I & Khazen A F H cemia and congestive heart failure Leb 20 69 1967
16 Scherf D Alterations in the form of the T with changes in heart rate Am Heart J 28 33
17 Schulman J L & Ratner H Idiopathi parathyroidism with bony demineralization a diac decompensation Pediatrics 16 848 1955
18 Troughton O & Singh S P Heart failu neonatal hypocalcaemia Br Med J 4 76 1972
19 Vincent G M Abildskov J A & Burges Q–T interval syndromes Prog Cardiovas D 523 1974
20 Zsigmond E K Hypocalcemic hypotension 226 355 1973

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Osteosclerotic Myeloma with Polyneuropathy

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STRACT Five cases of histologically verified ma cell myeloma in sclerotic skeletal foci and neuropathy are reported Thirty similar cases collected from the literature They illustrate a ial form of plasma cell neoplasia The charac tic features are osteosclerosis polyneuropathy nbling polyradiculitis approximately normal oglobin concentration bone marrow smears and low concentration of M protein and absence nce Jones proteinuria Slow progression of the se is a possible additional feature It is hy esized that autoimmune mechanisms are in d in the pathogenesis This hypothesis is based e observation of circulating immune complexes Ive Waaler s reaction and relative increase in the ber of circulating B-lymphocytes

words myeloma osteosclerosis polyneuropathy nology neurophysiology pathogenesis
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lomatosis and multiple myeloma are caused by gnant proliferation of plasma cells In most s the tumour cells belong to the same clone therefore produce uniform immune protein protein) The classical radiological features are r multiple minute foci giving the bone an os rotic appearance or larger osteolytic defects se are often circular and well defined with no ound ng sclerosis Treatment of such lesions by lation or cytotoxic agents may result in osteo rosis However rare cases with osteosclero- prior to treatment have been reported and markable number of them have also had rological changes consistent with polyneuro- y

e present five additional cases and discuss the tionsh p between the primary osteosclerosis polyneuropathy and other findings characteris f this syndrome

CASE REPORTS

Case 1

Female born in 1914 The first symptoms appeared late in 1966 with restless legs general weakness and difficulty in walking Within a few months she became totally unable to walk and lost a great deal of weight

Neurological examination in Jan 1967 showed a sensorimotor polyneuropathy with pareses hypoesthesia and hypoalgesia and absence of deep tendon reflexes in both legs The arms were not clinically affected except for weak deep tendon reflexes Roentgenogram revealed multiple osteosclerotic foci throughout the skeleton Histologically the foci contained atypical plasma cell infiltrates in cavities within sclerotic bone with thickened lamellae with many cement lines indicating periodic growth Between the normal bone and the plasma cell infiltrates there were concentrations of mature lymphocytes with lymph follicles The plasma cell infiltrates contained a homogeneous eosinophilic substance probably a result of globulin production Hb was 15 1 g/100 ml ESR 3 mm/hour Bone marrow smears showed less than 2% plasma cells Serum contained monoclonal IgG Lambda in low concentration EMG recorded in the right arm and both legs showed a peripheral neurogenic lesion The motor conduction velocity was slightly reduced in the right ulnar nerve and could not be recorded in the lower extremities because of atrophic musculature Spinal fluid protein concentration was 161 mg/100 ml The fluid did not contain cells Liver and kidney function tests were normal

The condition was considered to be a myeloma and treatment was started with melphalan and prednisone Melphalan was discontinued after a few months The neurological symptoms improved slightly with prednisone treatment until 1970 Prednisone was discontinued in 1975

In 1976 roentgenograms showed considerable reduction of the osteosclerotic foci and nearly normal bone structure Hb was 13 3 g/100 ml and ESR 4 mm/h No rheumatoid factor or immune complexes were found in the serum neither were immune complexes found in nerve and muscle biopsies There were 15% B lymphocytes and 37% T-lymphocytes in the blood Bone marrow liver and kidney function tests were normal The clinical findings have later remained virtually unaltered

Case 2

Male born in 1905 (previously publ shed by Sm th Meyer (54)) The d agnosis of myeloma based on b opsy from a *sclerot c rib les on was establ shed in 1956 The pat ent* was observed w thout any treatment unt l 1964 when a lam nectomy had to be performed because of tumour pressure on the sp nal cord produc ng pares s H s tolog cal exam nat on of the tumour showed h ghly cel lular t ssue w th large and pleomorph c plasma cells Hb was 1? g/100 ml ESR 14 mm/h

In the follow ng year the pat ent began to compla n of pain in hands and feet Roentgenograms showed sclerot c *lesions in the upper femur and iliac bone on the right side* and 4th lumbar vertebra Hb was 12 1 g/100 ml ESR ?0 mm/h There were 10% plasma cells some of them atyp cal in the sternal bone marrow smears He was treated w th melphalan for a short time In 1966 the pa n in hands and feet had increased and was espec ally local zed to the small jo nts Neurological exam nat on showed sen sorimotor polyneuropathy in arms and legs w th d stal pareses hypoesthes a and absent deep tendon reflexes *The legs were cyanot c and showed reduced arterial pul* sat on Roentgenograms showed scleros s n another r b Hb was 15 1 g/100 ml and ESR 11 mm/h Serum prote n electrophores s showed a small pathological fract on be tween the gamma and beta f elds mmune electrophores s showed *monoclonal IgA* kappa in *moderate* concen trat on EMG showed s gns of a peripheral neurogen c les on w th motor nerve conduct on veloc ty in the med an nerve reduced to 20 m/sec Throughout 1967 the *general cond t on worsened and the patient compla ned of* increased rheumato d pa n n knees ankles and feet Ac rocyanos s increased in hands and feet The neurological symptoms also increased A t b al muscle b opsy showed m scle cell atrophy Hb was 6 9 g/100 ml and ESR 80 mm/h In the sternal bone marrow smear there were 5–10% plasma cells

The pa ent d ed n 1968 of renal fa lure Autopsy d s closed multiple myeloma nf ltrat on in the skeleton The inf ltrat ons n the lumbar vertebra were surrounded by bone show ng several cement l nes but no scleros s The bone around the inf ltrations in the affected ribs was sclerot c However the cell types in these inf ltrates were of uncertain nature Plasma cell inf ltrates suggest ng myeloma inf ltrates *were found in enlarged lymph nodes* in the med ast num The kidneys showed s gns of chron c pyelonephrit s and the l ver and spleen were congested Amylo dos s could not be found

Case 3

Male born n 19 6 After some years w th period c low back pa n the patient was hosp tal zed n 1965 for nves t gat on of pa n and weakness n legs and hands The *musculature was sl ghtly atroph c Roentgenograms of the* sp ne were normal The sp nal flu d protein was 163 mg/100 ml with normal pressure The cond t on was con s dered to be a form of general zed myalgia and was treated w th phys otherapy

The pat ent was readm tted n 1966 Roentgenograms now revealed polycycl c osteolyt c destruct on n the sac rum with surround ng scleros s B opsy showed myeloma The sternal bone marrow smear was normal Elec trophores s showed sl ght ncrease of β-globul sacrum was irrad ated w th a dose of 3000 R.

In 1970 the pat ent developed sensorimo *neuropathy w th symmetrical pares s of di* most ma ked in the legs and w th absent dee reflexes There were hypoesthes a and hypoalge legs but no sensory changes in the arms Roen ge now showed increased destruct on of the um round ng bone was scle ot c Hb was 15 0 g/10 ESR 15 mm/h There were less than 5% pla m the sternal marrow smear Electrophores s show creased prote n component between the gamma f elds *Immune electrophores s showed two* ponents of IgA type (later exam nat on showed component IgA lambda) EMG and nerve veloc ty stud es were not carried out

After treatment w th cyclophospham de th scleros s ncreased the electrophores s curve normal and the pareses improved The mp ove t nued after replacement of cyclophospham de phalan

Reexam nat on n 1977 st ll showed b la eral but there were normal deep tendon reflexes n Roen genograms showed unchanged scleros s n Hb was 15 0 g/100 ml ESR 4 mm/h l ver funct on tests were normal Electrophores s and *electrophores s were normal* Rheumato d facto clear factor and an DNA were not found Musc from the leg showed atroph c f bres w thout a plasma cell nf ltrates There was no amylo d b opsy Ingu nal lymph node b opsy showed structu e The pat ent has been in full t me wor last years

Case 4

A female born in 1913 had for several years from low back pa n and had a trans ent rig paralys s n 1960 In early 1974 she developed p sensorimotor polyneuropathy w th symme rica pares s n legs and arms She had hypoe hes a deep tendon reflexes were absent Oph halm showed early pap lledema Roentgenograms show t ple dense sclerot c foci in the skeleton These c seen on earl er f lms as far back as 1972 *Hb was l ml ESR 8 mm/h No rheumato d factor* was d Lumbar sp nal flu d showed normal pressu e pro g/100 ml and normal cell count Immunoelectrop showed monoclonal IgG lambda n low concent n serum and sp nal flu d EMG showed a per neurogen c les on n the right leg and arm *Mo or c* t on veloc ty n the right ulnar nerve was 23 m/sec bra n scan pneumoencephalography cerebral graphy and myelography were normal

Progress on of the pareses and the sclero c foc s n the spring of 1975 (F g 1) Pedal lymphography sh defects of uncerta n s gn f cance n mul ple lymph Hb fell to 9 2 g/100 ml and ESR rose to 54 mm/h sp nal prote n rose to ?32 mg/100 ml although th count was *st ll normal A b opsy of a sclerotic costal* showed plasma cell nf ltrat on surrounded by dense lect ons of lymphocytes adjacent to extensive sc areas of bone w th mul ple cement lines The lesion



Fig 1 Case 4 1975 Osteosclerotic skeletal myeloma foci

...dered to be a myeloma A lymph node biopsy dem...ra ed dense plasma cell infiltrat on probably of ...her than neoplast c nature

...cond tion stab lized and from the summer ...975 onwards some mprovement during chemotherapy c) lophosphamide and predn sone was noted and al o w th procarbaz ne n add t on The mprove...t ceased after a short wh le and the chemotherapy ...d scontinued Later in 1975 her hands st ll showed ...tractures with paresis Hb was 9 3 g/100 ml and ESR ...m/h Serum creat n ne was sl ghtly elevated and there ...s ght prote nuria w thout any s gn of Bence Jones ...e n The spleen was enlarged on isotope scans Mus...biopsy showed neurogen c atrophy The rectal mucosa ...h stologically normal The patient s serum contained ...ma o d factor (Waaler t ter 256 Latex ++) and ...e were c rculat ng immune complexes in moderate ...s Of the blood lymphocytes 49% were B and 36% ...mphocytes Immune complex depos ts were not ...nd in nerve and muscle b opsies

...he general cond t on deteriorated during the spring of ...6 and the neurolog cal s gns progressed Roentgeno...ms showed increased skeletal involvement partly os...lytic partly osteosclerot c In early 1978 the patient ...eloped edema lung inf ltrates and bilateral pleural ef...ion containing atyp cal plasma cells The sclerotic foci ...he skull disappeared Finally the Hb fell and the ...ent d ed in 1978

...e 5

...le born in 1931 Throughout many years he had had ...ated attacks of urol thias s and had s nce 1968 been ...d for hypertens on Late in 1975 he developed ...orbital edema and edema of the hands and feet In 1976 he progress vely developed a polyneuropathy w th d stal and symmetrical pareses in the legs The deep tendon reflexes d sappeared n bo h legs and arms There was no sensory loss In the spring of 1976 he developed jo nt pa ns and morn ng stiffness n the hands The pareses progressed and hypoesthes a developed f rst in the legs and later n the arms During the night he sweated and had ch lls The small f nger jo nts became swollen and the l...er enlarged Roentgenograms showed enlargement of the heart and pulmonary congest on A sclerot tumou... a... apparent on X ray of the left half of the pelv... On earlie... f lms the tumour could be seen as far back as 1970 B opsy showed plasma cell myeloma A homogeneou... eosinoph l c substance poss bly local globul n was found in the s nusoids n the tumour tissue B opsy of the n... gu n...l lymph nodes and from the rectal mucosa showed dense plasma cell inf ltration Hb was 14 7 la er 11 9 g/100 ml ESR was 41 later 56 mm/h Serum electrophores s showed elevated β-globulin Immune electrophoresis revealed a low concentrat on of monoclonal IgA with indef nable light chains Tests for rheumato d factor were pos t ve (Waaler t ter 256 Latex ++++) Bone marrow smears were normal The liver and spleen were enlarged on isotope scans Lymphography showed mult ple defects in the lymph nodes as seen in lymphoma Serum creat n ne was 1 8 later 2 9 mg/100 ml There was sl ght proteinuria without Bence Jones prote n Lumbar spinal flu d showed a prote n concentrat on of 99 later 146 mg/100 ml EMG showed a peripheral neurogen c les on The motor nerve conduct on veloc ty was 17 m/sec in the peroneal nerve The tumour area in the pelvic bones and the il acal and lumbar lymph nodes were treated with external rad otherapy to a dose of 40 Gy In add t on combination chemotherapy was started w th cyclophospham de procarbazine and predn sone H s conges t ve heart fa lure was treated with d gitox n and d uret cs

A

Case 2

Male born in 1905 (previously published by Smith Meyer (54)) The diagnosis of myeloma based on biopsy from a sclerotic rib lesion was established in 1956 The patient was observed without any treatment until 1964 when a laminectomy had to be performed because of tumour pressure on the spinal cord producing paresis Histological examination of the tumour showed highly cellular tissue with large and pleomorphic plasma cells Hb was 12 g/100 ml ESR 14 mm/h

In the following year the patient began to complain of pain in hands and feet Roentgenograms showed sclerotic lesions in the upper femur and iliac bone on the right side and 4th lumbar vertebra Hb was 12 1 g/100 ml ESR 20 mm/h There were 10% plasma cells some of them atypical in the sternal bone marrow smears He was treated with melphalan for a short time In 1966 the pain in hands and feet had increased and was especially localized to the small joints Neurological examination showed sensorimotor polyneuropathy in arms and legs with distal pareses hypoesthesia and absent deep tendon reflexes The legs were cyanotic and showed reduced arterial pulsation Roentgenograms showed sclerosis in another rib Hb was 15 1 g/100 ml and ESR 11 mm/h Serum protein electrophoresis showed a small pathological fraction between the gamma and beta fields immune electrophoresis showed monoclonal IgA kappa in moderate concentration EMG showed signs of a peripheral neurogenic lesion with motor nerve conduction velocity in the median nerve reduced to 20 m/sec Throughout 1967 the general condition worsened and the patient complained of increased rheumatoid pain in knees ankles and feet Acrocyanosis increased in hands and feet The neurological symptoms also increased A tibial muscle biopsy showed muscle cell atrophy Hb was 6 9 g/100 ml and ESR 80 mm/h In the sternal bone marrow smear there were 5–10% plasma cells

The patient died in 1968 of renal failure Autopsy disclosed multiple myeloma infiltration in the skeleton The infiltrations in the lumbar vertebra were surrounded by bone showing several cement lines but no sclerosis The bone around the infiltrations in the affected ribs was sclerotic However the cell types in these infiltrates were of uncertain nature Plasma cell infiltrates suggesting myeloma infiltrates were found in enlarged lymph nodes in the mediastinum The kidneys showed signs of chronic pyelonephritis and the liver and spleen were congested Amyloidosis could not be found

Case 3

Male born in 1926 After some years with periodic low back pain the patient was hospitalized in 1965 for investigation of pain and weakness in legs and hands The musculature was slightly atrophic Roentgenograms of the spine were normal The spinal fluid protein was 163 mg/100 ml with normal pressure The condition was considered to be a form of generalized myalgia and was treated with physiotherapy

The patient was readmitted in 1966 Roentgenograms now revealed polycyclic osteolytic destruction in the sacrum with surrounding sclerosis Biopsy showed myeloma The sternal bone marrow smear was normal Electrophoresis showed slight increase of β-globul[illegible] sacrum was irradiated with a dose of 3000 R

In 1970 the patient developed sensorimot[illegible] neuropathy with symmetrical paresis of dist[illegible] most marked in the legs and with absent dee[illegible] reflexes There were hypoesthesia and hy[illegible] legs but no sensory changes in the arms Roentg[illegible] now showed increased destruction of the ilium [illegible] rounding bone was sclerotic Hb was 15 0 g/10[illegible] ESR 15 mm/h There were less than 5% plasm[illegible] the sternal marrow smear Electrophoresis [illegible] creased protein component between the gamma [illegible] fields Immune electrophoresis showed two [illegible] ponents of IgA type (later examination sh[illegible] component IgA lambda) EMG and nerve [illegible] velocity studies were not carried out

After treatment with cyclophosphamide th[illegible] sclerosis increased the electrophoresis curve [illegible] normal and the pareses improved The [illegible] tinued after replacement of cyclophospham[illegible] phalan

Reexamination in 1977 still showed bilateral [illegible] but there were normal deep tendon reflexes in [illegible] Roentgenograms showed unchanged sclerosis [illegible] Hb was 15 0 g/100 ml ESR 4 mm/h liver [illegible] function tests were normal Electrophoresis and [illegible] electrophoresis were normal Rheumatoid facto[illegible] clear factor and anti DNA were not found Musc[illegible] from the leg showed atrophic fibres without a[illegible] plasma cell infiltrates There was no amyloid i[illegible] biopsy Inguinal lymph node biopsy showed [illegible] structure The patient has been in full time wo[illegible] last years

Case 4

A female born in 1913 had for several years [illegible] from low back pain and had a transient rig[illegible] paralysis in 1960 In early 1974 she developed pro[illegible] sensorimotor polyneuropathy with symmetric[illegible] paresis in legs and arms She had hypoesthesia [illegible] deep tendon reflexes were absent Ophthalm[illegible] showed early papilledema Roentgenograms show[illegible] tiple dense sclerotic foci in the skeleton These [illegible] seen on earlier films as far back as 1972 Hb was 1[illegible] ml ESR 8 mm/h No rheumatoid factor was de[illegible] Lumbar spinal fluid showed normal pressure pro[illegible] g/100 ml and normal cell count Immunoelectrop[illegible] showed monoclonal IgG lambda in low concen[illegible] in serum and spinal fluid EMG showed a per[illegible] neurogenic lesion in the right leg and arm Motor co[illegible] tion velocity in the right ulnar nerve was 23 m/sec [illegible] brain scan pneumoencephalography, cerebral [illegible] graphy and myelography were normal

Progression of the pareses and the sclerotic foci s[illegible] in the spring of 1975 (Fig 1) Pedal lymphography sh[illegible] defects of uncertain significance in multiple lymph [illegible] Hb fell to 9 2 g/100 ml and ESR rose to 54 mm/h [illegible] spinal protein rose to 232 mg/100 ml although th[illegible] count was still normal A biopsy of a sclerotic costal [illegible] showed plasma cell infiltration surrounded by dense [illegible] lections of lymphocytes adjacent to extensive scle[illegible] areas of bone with multiple cement lines The lesio[illegible]

able I Ma n feat es f r f e cases l f 30 c ses r ported b tl ers

Pre ent absen ↑ eleva ed N normal

	Our cases					30 Ca es collected f om he l era u e		
	1	?	3	4	5	No mal	Pathol	No nd ca ed
s eo cle os s	+	+	+	+	+		30	
yneuropa hy	+	+	+	+	+		30	
one le on b opsy—myeloma	+	+	+	+	+		All ca es	
ymph node b op y—myeloma		+		(+)	(+)		h stologically	
c um b ops —myeloma					(+)		enf d	
asma ce s n marrow as ıra on smears (%)	<?	≈10	<5	<3	<?	0	*	8
R at the me of d agnos s mm/h)	3	15	15	8	41	16	1	13
a he me of d agnos /100 ml)	15	1	15	13	15			
nem a						18		10
pe of monoclonal serum ro e n	IgGλ	IgAχ	IgAλ	IgGλ	IgA	8	9	13
nce Jones pro e nuria						1	3	6
onoclonal urine p o e n	(+)			+				
reb o p nal flu d p ote n	↑	↑	↑	↑	↑	0	3	7
noclonal sp nal flu d p o e n	(+)			+		1	1	8
reb o p nal flu d cells 0⁶ l)	N	N	15	N	N	17	1	1
euma o d fac o (Waa er)				+	+			
F anti DNA	–							
cu a ng mmune complexes				+	+			
culating B-lymphocytes (%)	50			49	?5			
enomegaly (o ope scans)	+			+	+			
e oma n enlarged spleen u op y)								

eferences 1 4 13 17 ?1 6 28 9 30 3 34 37 38 39 44 46 47 48 49 50 53 55 56 57 6?

ca es normal or be ow 2% 5 cases not cons stent w th myeloma or below 7% Two of he e ca es had po e
arrow b opsy one of them eleva ed ESR as well

ne ca e 0 mm/h one 15 mm/h the others below

o e bone marrow smea Hb 7 6 g/100 ml and o teolyt c les ons as we l

ca es above 17 g/100 ml and one polycythemic case

ne case 7 6 and one 11 8 g/100 ml

ca es w th IgA 6 w h IgG and one case w h Bence Jones p o e n n serum

7 ca es abo e 100 mg/100 ml one had flu d blockade

) 10⁶ ce /l

oderate (Table I) Hb rema ned normal for a long riod but anem a and elevated ESR developed in es ? and 4 shortly before death Extens ve mar w nfil rat on w th low Hb and elevated ESR has en reported almost exclusively n the term nal ge (0 41 55) Thus bone marro v smears are ually no mal although posit ve b ops es are ob ned f om the sclerot c skeletal foci The marrow olvement is apparently focal rather than d ffuse d may be m ssed by the usual bone marrow smear ocedure We therefore prefer the term os sclero c myeloma nstead of osteosclerotic elomatos s

Relat o ı bet een tl e n a feat es

We have collected from the l terature 30 el d cu mented cases of osteosclerot c myeloma w th polyneuropathy The characterist c features of our five cases correspond well w th tho e of these pat ents (Table I) and we agree that the pat ents demonstrate a spec al form of monoclonal plasma cell neoplas a (35 57 59) On the bas s of h stolog cal exam nat on we bel e e that the cases are real myelomas and not results of secondary plasma cell react ons

The characterist c features nclude osteosclerot c skeletal myeloma foci a polyneuropathy re

Heynen G & Salmon J Osteosclerotic myeloma with polyneuropathy and ectopic secretion of calcitonin Eur J Cancer 14 133 1978

47 Rowland L P & Schneck S A Neuromuscular disorders associated with malignant neoplastic disease J Chron Dis 16 777 1963

48 Rushton D I Peripheral sensorimotor neuropathy associated with a localized myeloma Br Med J 2 203 1965

49 Scott L Unpublished case 1960 Quoted in ref 58

50 Shimomori T & Kusumoto M A case of solitary plasmacytoma with polyneuropathy pigmentation and gynecomastia (abstract) J Jpn Soc Intern Med 59 1008 1970 Quoted in ref 25

51 Sigwald J & Nouailhat F The Guillain Barré syndrome In Handbook of clinical neurology vol 7 (ed P J Vinken & G W Bruyn) p 495 North Holland Publishing Co Amsterdam 1970

52 Silverstein A & Doniger D E Neurologic complications in myelomatosis Arch Neurol 9 102 1963

53 Small J M Moxon C P & Woolf A L Report on a clinico pathological conference Bgham Med Rev 20 546 1961

54 Smith Meyer R Osteosclerose ved myelomatose Nord Med 77 747 1967

55 Talerman A & Bateson E M Multiple myeloma associated with bone sclerosis an[d] neuropathy Br J Radiol 43 698 1970

56 Victor M Banker B Q & Adams neuropathy of multiple myeloma J Neuro[l] Psychiatry 21 73 1958

57 Waldenstrom J Die Formenkreise d[es] zytoms Schweiz Med Wochenschr 100 7[...]

58 — Diagnosis and treatment of multiple my[eloma] 53 Grune & Stratton New York and Lond[on]

59 Waldenstrom J Adner A Gydell K [...] vall O Osteosclerotic plasmocytoma [...] neuropathy hypertrichosis and diabetes Med Scand 203 297 1978

60 Warner N L Potter M & Metcalf D (ed[s]) [Mul]tiple myeloma and related immunoglobulin[...] neoplasms UICC Techn Rep vol 13 UICC [...] 1974

61 Wegelius O Skrifvars B & Ande[rsson] Rheumatoid arthritis terminating in plas[mocytoma] Acta Med Scand 187 133 1970

62 Yodoi J Takatsuki K & Wakisaka [...] sociation of atypical myeloma polyneuropa[thy] mentation and gynecomastia A possible [...] drome (abstract) Acta Haematol Jpn 36 36[...] Quoted in ref 25

ANNOUNCEMENT

International Symposium on Calcium Antagonism in Cardiovascular Therapy Experiences with Verapamil will be held in Florence Italy Oct 2–4 1980 *Organizing Secretariat* AISC Assistenza Internazionale [...] Congresso Via G B Martini 6 Rome Italy

EORT NCI Symposium on Nutrition of the Cancer Patient will take place in Brussels Be[lgium] Jan 8–9 1981

The program will include invited presentations and free communications Abstracts (200–250 words) must be submitted by Nov 15 1980 and should be sent to Dr Daniel L Kisner EORTC Data Center In[stitut] Bordet 1 rue Héger Bordet 1000 Bruxelles B[elgium]

Structure and Function of Neutrophil Leukocytes from Patients with the Immotile Cilia Syndrome

Bjorn A Afzel us Lena Ewetz Jan Palmblad Ann Mari Uden
and Nikolaos Ven zelos

om We ner G en Inst te Un ers ty of Stockl oln S ed sl Nat onal Defence Researcl Inst t te S ndb berg F th Depa tment of M d c ne and Departn ent f Cl n cal M crob ology Ka l nska Ins tute at S derssj kl uset St ckl oln S eden

STRACT The various clinical manifestations of recently characterized immotile cilia syndrome i be traced to one cause—a structural defect of the a making them immotile It was regarded of in est to examine whether other aspects of cell motili also be involved For this reason the functions l structure of the neutrophil leukocytes were mined Cells from eight patients with the im tile cilia syndrome and healthy controls were in tigated with regard to random and stimulated motion under agarose orientation during mi tion adherence bactericidal capacity and chemo-luminescence Four patients showed abnormally rt migrat on distances of the lead ng front neu ls after st mulation with serum and/or an E bacterial factor (BF) Ascorbic acid did not re re the defective migration Migrating neutrophils re signif cantly less oriented towards the serum taining agarose well compared with the controls 0 01) Adherence bactericidal capacity for phylococcus aureus chemoluminescence random grat on and orientation during BF induced migra n were all normal The number of microtubules in pericentriolar region of the neutrophil granulo-es was unusually low in four of the eight patients e conclude that the increased frequency of res ratory tract infections in patients with this syn ome is possibly due to defects in the granulocyte ry system as well as to the defective icociliary clearance of the airways

Key words chemotax s neutroph ls bacteric dal capaci Kartagener triad m crotubules
a Med Scand 08 145 1980

ubules together with m crofilaments are dered to be respons ble for cell locomotion)) Thus cil a and sperm ta ls are capable of mo- because adjacent m crotubules can slide along each other in these organelles This movement de pends on the repeated mak ng and breaking of bonds made by a prote n called dynein (29) Dyne n is a h gh molecular weight protein and is vis ble in the electron microscope because it forms protru s ons from the microtubules which seem to l nk them together (29) The protrus ons are called dy nein arms and are arranged along the outer mi crotubules wh ch are also connected by the so-called spokes If dyne n arms or spokes are ab- sent in the cil a (and the sperm ta ls) these are unable to move (1 2 11) The resulting decreased tracheobronchial clearance of dusts and microor gan sms accounts for the recurrent resp ratory tract infections in patient with what has been called the immotile c l a syndrome (ICS) (1 2 11) Th s may also include s tus inversus and bronch ectas s and is then called Kartagener s syndrome

The mechanisms beh nd granulocyte mot l ty are not kno vn but m crotubules extending from the centrioles are believed to play a rol (18 30) In particular an intact microtubular system seems to be necessary for an oriented locomotor response to cytotaxins (18) Also the adhesiveness of the leukocytes and their phagocytic capacity have been suggested to depend on microtubules (6 8 14) However it is not known whether dynein arms are crit cal for the funct ons of neutroph ls

The aim of the present study was to find out

Abbre at ons BF bacterial factor ICS immotile c l a syndrome PMN polymorphonuclear granulocyte

The results were presented in part at the Annual Meet ng of the Swed sh Med cal Assoc at on Dec 1978 and at the Int Congr of Haematology Hamburg West Germany 1979

Table I *Clinical data on eight patients with the immotile cilia syndrome*

Case numbers are the same as in ref 11 and 19 except for patient 15 not described before Cases 1 and 2 are brothers *Sperm tails from case 4 were normally equipped with dynein arms but lacked probably radial spokes Dynein arms were present in sperm tails from case 14* but probably in reduced numbers

Case no	Sex	Age (y)	Recurrent infections	Infertility	Situs inversus
1	♂	40	+	+	+
2	♂	34	+	+	−
3	♂	35	+	+	+
4	♂	35	+	+	−
7	♀	30	+	?	+
13	♀	29	+	?	+
14	♂	35	+	+	+
15	♀	29	+	?	+

whether orientation during neutrophil locomotion stimulated and random migration bactericidal capacity, chemoluminescence and adherence are abnormal in patients with documented ICS including ultrastructural defects of the dynein arms or radial spokes We have also attempted to relate the migratory responses of the neutrophils to the number of centriole associated microtubules determined by electron microscopy

STUDY POPULATION AND METHODS

Patients Eight patients (5 men 3 women) with documented ICS were investigated with respect to their neutrophil function Further details of the patients described in previous publications (11 19) are given in Table I All patients exhibited no or low tracheobronchial clearance six lacked dynein arms one had reduced numbers in cilia and/or sperms and one lacked axonemal spokes All had a history of recurrent infections of the upper and lower airways with chronic expectoration of mucopurulent sputum Patient 3 has a massive history of allergy previously associated with asthma and now with generalized eczema He has been treated with steroids but not l

All patients with recurrent infections were freq treated with antibiotics mucolytics and theophyll derivates All drugs were however withdrawn for a two days prior to blood sampling None had recent an infection as evidenced by the case history and ESR (2–16 mm/h in all except patient 3) All had n Hb concentrations leukocyte counts serum electro liver and renal function tests and urinanalyses Pa had slightly elevated S ASAT and S ALAT level albuminuria his other laboratory tests were normal

The study included paired healthy age and matched controls In addition to these controls b blood bank donors were used for comparison

Leukocyte preparation Erythrocytes in hepa blood (10 IU heparin (without preservative) per ml were sedimented in 4 5% dextran T 500 and the leuk supernatant was centrifuged at 500 g for 6 min The *lar pellet was washed twice in heparinized 0 9% sa* IU heparin per ml saline) and the leukocytes were pended either in Hank s balanced salt solution con 0 1% gelatin for the bactericidal and chemolumines assays or for the chemotaxis assays in a 3 1% buffer (Sigma St Louis Mo USA) dissolved in 199 medium (State Bacteriological Laboratory holm) to make appropriate neutrophil concentration

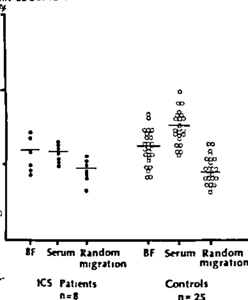
Neutrophil assays The bactericidal capacity analysed as described previously (22) In short n phils were mixed with suspensions of Staph aure serum The mean concentrations in the test tube were 2 5×10⁹/l (range 2 2–2 8) of bacteria 1 0×10 ony forming units/l and of serum 10% After 45 min incubation at 37°C samples were removed for tation of viable bacteria The results are given a percentages of living bacteria after 45 and 90 min cubation of the initial counts The reference values lished on the basis of analyses of 103 healthy blood donors are given in Table II The reproducibility method has been presented elsewhere (23)

The granulocytic oxidative metabolism was quan with the luminol augmented chemoluminescence a scribed previously (12) Granulocytes (2 5×10⁹/l) (10%) living Staph aureus (70×10⁹/l) and lu (2 6×10⁻⁴ M) were incubated for 20 min at 37°C maximal chemoluminescence was then measured photomultiplicator and the results are expressed in m

Adherence was assayed by the nylon fiber co method described by MacGregor et al (17) and Palm et al (24) The results are given as the percentag neutrophils adhering to the fibers The reference va

Table II *Neutrophil functions in patients with the immotile cilia syndrome and in controls (mean±S*

	Patients	Controls	Reference values (mean±2 S D)
Bactericidal capacity (% colony forming units)			
After 45 min	5 3±1 9	4 9±1 8	2 7–14 8
After 90 min	2 3±1 2	2 2±0 8	0 5–5 4
Chemoluminescence (mV)	188±48	207±52	Not established
Adherence (%)	53±18	41±22	22–95



…1 Percentage migrating granulocytes showing orien… The mean variation of the determination is 5%. A …stically significant difference was noted between pa…ts and controls when migration was induced by serum …01). In the extended control series orientation dur…g migration towards serum is significantly higher …001) than towards the bacterial factor (*BF*) and dur… spontaneous migration ($p<0.001$).

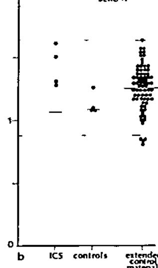
given in Table II. The mean day-to-day variation (S.E. value) for a single subject is 5%.

The random migration and stimulated locomotion induced by two cytotaxins were assayed with a modification of a method measuring neutrophil migration under agarose (20, 28). Briefly, an agarose solution, with a final albumin concentration of 0.08%, was allowed to gel in Petri dishes. Six series, each consisting of 3 wells, were punched in the agarose. The diameter of one well was 3 mm and the distance between the centers of two adjacent wells 5 mm. A 10 μl sample of a leukocyte suspension containing approximately 10×10^9 neutrophils/l (range 8.5–12.7) was filled in the central well. Chemotactic factors, either a sterile E. coli bacterial filtrate (BF) (24) or pooled human AB serum (22) were filled in the outer well. Tissue culture medium was added to the inner well.

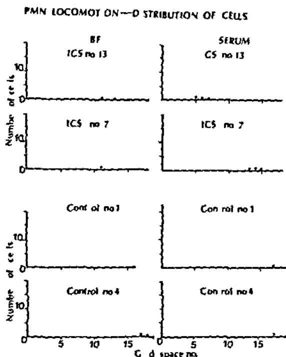
The dishes were incubated for 3 hours at 37°C in an atmosphere of 5% CO_2. After fixation with methanol and staining with hematoxylin and fuchsin, the agarose dishes were removed and the distance migrated by the leading front neutrophils was measured by microscopy and given in mm. In addition, we counted the number of cells migrating towards the chemotactic factors and towards the tissue medium using an ocular containing a grid of vertical and horizontal lines (21). The number of cells within each grid space was counted and the location of the maximal cell density, i.e. the grid space containing the highest number of cells, was determined.

The orientation of lamellopodia and nuclei of 600 neutrophils migrating towards the cytotaxin and tissue medium wells was estimated by microscopy for each subject. The cells were considered polarized in the gradient when





…2. Stimulated and spontaneous locomotion of neu…phils from patients with the immotile-cilia syndrome, …ched controls, and extended control series, measured …the leading front technique. (*a*) Spontaneous and BF …uced locomotion. --- = Reference values (±2 S.D.) for the extended control series: for BF induced locomotion they are 0.65–1.34 mm and for spontaneous locomotion 0.09–0.28 mm. (*b*) Serum induced locomotion. The reference value for the latter (---) is 0.88–1.63 mm.



F g 3 Number of cells w th n each grid space n two pat ents and two controls calculated as described by Orr and Ward (21) The border of grid space 1 touches the neutroph l well and the space w th the h ghest number s closest to the cytotax n well

the nucle were n the rear and the anterior lamellopod a located w h n a 90° sector open towards the cytotax n well The orientat on of m grat ng neutroph ls from 25 healthy donors nclud ng the ma ched control are shown n F g 1

No d fference in the d stance to the lead ng front or the locat on of max mal cell dens ty was found when neu troph l suspens on concentrat ons varied between 7 and 16×10⁹/l The day to-day variat on (S D n per cent of mean) of granulocyte m grat on for three subjects assayed as above s 6 5 The reference values for neutroph l m gra on measured as the lead ng front were establ shed from the analyses of apparently heal hy blood bank donors and members of the laboratory staff and are gi en n F g 2

Neutroph ls from pat ents and controls were also ncu bated w th ascorb c ac d 10 mmol/l (Merck Darmstadt Germany) at 37°C for 15 m n pr or to appl ca on n the agarose d sh w th BF as chemoa tractant St mulated and random m grat on assessed as above w th the lead ng front d stance were compared w th cells trea ed n a s m lar way except for ascorb ac d

Electron m croscop cal m ethods Leukocyte prepara t ons from pat ents and controls were processed w th iden t cal techn ques and at the same occas ons Primary f xa t ve was n 4% glutaraldehyde n 0 05 M cacodylate buffer to wh ch 0 015% calc um chloride and 4% su rose had been added After f xat on the samples were rinsed in the buffer postf xed in a 1% osm um tetrox de solut on n the same buffer dehydrated n a graded ethanol series and embedded n Epon 812 Sect ons we e cut a a f rotome sett ng (600 Å) and section sta ned in a s ized fash on w th uranyl acetate and lead c ra e

The number of m crotubules was recorded as f Granulocytes wh ch had been sect oned at the le e or both centr oles were re orded n the electron scope at a magn f cat on of ×15000 Th s magni was too low to perm t the m croscop st to select m crotubules yet h gh enough to perm a cou the r number n the (three t mes) enla ged phot papers The area of cytoplasm a ound the centri recorded s 15 μ Coded spec mens we e s udied electron m croscop st to further perm t a non bias pl ng

RESULTS

Neutroph ls from the pat ents showed a s a sign f cant decrease compared w th the con their or entat on to vards the serum-con cytotax n well ($p<0.01$ Mann Wh tney t Or entation towards the BF conta n ng we s m lar in pat ents and controls ($p>0.05$) A there was no stat st cally s gn f cant dif ($p>0.05$ Mann Wh tney test) between the pa red controls and the extended contr w th regard to locomot on distances ad chemolum nescence and bacteric dal capaci ble II) several patients showed values out reference values for neutroph l locomotion ured as the distance to the lead ng fron neutroph ls from pat ents 7 and 13 were bel reference values for m grat on induced by BF 2a) from pat ents 13 and 14 they were bel from patient 3 on the lower l m t of the ref values for locomot on induced by serum (Fig On the other hand patient 1 showed a h gh ra mob l ty and BF induced m grat on (Fig a) four of the e ght pat ents exhib ted abnormal cell locomotion after stimulation w th BF a serum Wh le one patient demonstrated lo comotion induced by both cytotax ns the three had low values for either BF or serum

After st mulat on with ascorb c ac d the di to the lead ng front was not more enhanced in of the ICS patients than n the control

The d stribut on of cells along the m grating was determ ned for pat ents and controls Th ues for two pat ents and two controls are show Fig 3 The locat on of max mal cell den assessed from determ nat ons of th s kind w yielded a lower m grat on for pat ents 7 and 13 for any control subject s neutroph ls when





4 and 5 Transversely sectioned centrioles in neu ils from patient 2 (Fig 4) and a healthy control (Fig one cell some microtubules run parallel with the triole and hence appear cross-cut (arrow heads) in the they run perpendicular to the centriole and are seen in longitudinal views (arrows) No systematic difference was found in orientation of microtubules or appearance of centrioles between patients and controls Magnifications ×63 000 (Fig 4) ×67 500 (Fig 5)

was induced by BF and similarly for patient 13 on migration was induced by serum

Morphological data The neutrophils had essen ly the same ultrastructure as described by ch et al (18) and will not be presented in detail e Our findings differed somewhat from those of lech et al (*a*) The system of filaments with a of about 10 nm (called thick filaments by lech et al and intermediate filaments or inter diate sized filaments by most others) formed es rather than isolated strands in cells in ich they occurred Such bundles were seen in trophils both from controls and ICS patients e significance of these filaments and of the differences in their arrangements is not understood and will not be discussed further (*b*) The number of microtubules per unit area around the centrioles was lower than in their study A possible explanation is that we examined the ultrastructure of un stimulated neutrophils whereas Malech et al studied stimulated ones The specimen preparation technique is also likely to influence the number and appearance of the microtubules

The centrioles and the microtubules around them were studied in further detail Like in other types of cells the centrioles consisted of nine microtubular triplets surrounded by an amorphous substance (Figs 4–5) There were lateral extensions from one





F gs 6 and 7 Pa rs of centr oles n neutroph ls from two controls In one cell the two centr oles have parallel axes (F g 6) n the other they are at r ght angle to each other F g 7) There was no systemat d fference between pa t ents and controls w h respect to orientat on of cent oles relat ve to each other or relat ve to the clo e es lobe The longest cent ole n F g 6 has la eral p t ons centr olar satell tes (arrows) *IF* = some r med ate f laments Magn f cat on ×49 500

of the centr oles so called centr olar satell tes (Fig 6)

Special attent on was pa d to the or entat on of the centrioles In the control group as well as in the patient group the two centrioles could lie more or less in l ne (Fig 6) or be perpend cular to each other (Fig 7) Nor was the or entation of the centrioles relative to the nearest nuclear lobe found to be constant

The centr oles were surrounded by a f nely granu lar reg on from wh ch ribosomes and other organ elles were excluded Some m crotubules could be seen in this reg on although most of them seemed to orig nate from the d stal port ons of the satell tes and rad ate outwards The per centriolar m tubules recorded as specified in Method counted and the absolute numbers and percent are g ven in Table III

Another way of express ng the number of crotubulues is to give the med an number of crotubules in the exam ned neutroph ls from e subject They were 0 5 1 1 1 5 ? 5 and ? (r controls and 0 0 0 0 1 1 ? and 3 for the patients Patient 14 (with a low mot l ty score the highest value 3 and pat ents 3 and 7 (al o low mot l ty scores) had 0 It s to be no ed the four lowest med an values were found in pat ent group It can be calculated that there

ɔle III *Number of microtubules (MT) in the pericentriolar region*

	Neutrophils with												
	0 MT		1 MT		2 MT		3 MT		4 MT		>4 MT		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	(*n*)
ts													
	9	60	2	13	1	7	0	0	0	0	3	20	21
	14	67	0	0	2	9	1	5	2	9	2	9	21
	11	85	0	0	1	8	0	0	0	0	1	8	13
	5	24	4	19	4	19	2	9	3	14	3	14	21
	15	60	2	8	2	8	0	0	4	16	2	8	25
	5	38	3	23	1	8	1	8	2	15	1	8	13
	1	7	2	13	2	13	3	20	1	7	6	40	15
	4	40	3	30	1	10	1	10	0	0	1	10	10
ols													
	2	13	3	19	3	19	1	6	1	6	6	38	16
	0	0	1	10	4	40	2	20	2	20	1	10	10
	7	44	3	19	2	13	2	13	1	6	1	6	16
	4	40	1	10	1	10	2	20	2	20	0	0	10
	7	44	5	31	1	6	2	13	0	0	1	6	16
	5	50	3	30	1	10	0	0	1	10	0	0	10

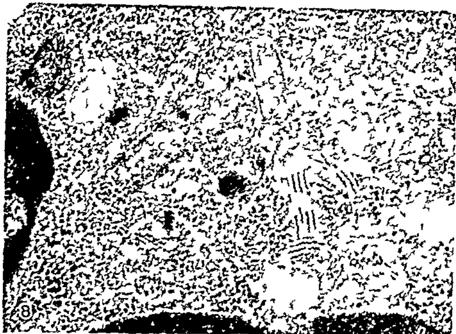
probability that chance alone is the reason for our lowest median values being found in the pa group The difference between the two groups t statistically significant although large enough worthy of a further investigation

though not of interest for the main topic of this it may be mentioned that so called parallel lar arrays were found in the lymphocytes from nts 7 13 and 14 (Fig 8) but not in lymphocytes the controls This is mentioned here because it been suggested that these parallel tubular arrays haracteristic of lymphocytes from persons who been treated with steroids (25 26) At least nts 2 and 14 deny having been on such therapy

DISCUSSION

is characterized by immotile cilia in the air s immotile sperms in males and often situs rsus (Kartagener s syndrome) leading to de sed resistance to infectious agents entering the ays and also to male infertility Some ultra ctural abnormalities have been suggested to be cause of the immobility such as absence of in arms or spokes between the microtubules (1 11 31) The patients studied here had such ormalities documented previously (1 11) he present study has shown that additional de s may also be present in some ICS patients A significantly lower mean rate of orientation in the serum gradient a low number of centriole associated microtubules in the resting granulocytes in some of these patients and an abnormally short distance migrated by neutrophils from 4 out of 8 tested patients point at a more widespread defect of the cytoskeleton than previously anticipated The defective neutrophil orientation and migration might also help to explain the increased susceptibility to infectious agents in the airways eventually leading to bronchiectases

Previous studies on patients with ICS and/or Kartagener s syndrome have focused mainly on the ultrastructure and function of cilia and sperms (1 2 3 11 27 31) However some studies of neutrophil functions have been reported Lupin and Misko (16) noted that the bactericidal capacity was slightly reduced in their two patients with ultrastructurally abnormal cilia Caleb et al (9) reported a case with situs inversus repeated infections and defective neutrophil chemotaxis They suggested that defects of the centriole or dynein arms could possibly account for their findings although they did not report any studies of the ultrastructure or function of cilia and neutrophils Hence as the present study demonstrated migratory defects were found in neutrophils from half of the patients with a well defined ciliary immotility whereas no defects of the bactericidal mechanisms were noted The reason for



F\ 8 Two cen n and some parallel t rays ın a lymphoc\ pat ent 14 Such ar bel eved to be more n persons who ha ce ved stero d trea th s pat ent has e rece ved such t eat Magn f cat on ×48

this discrepancy from the other Kartagener patients described by Lupin and Misko is not known

The role of m crotubules for leukocyt c funct ons have been documented in several ways In e g Ched ak H gashi s d sease a suggested defective assembly of m crotubules in leukocytes results in low chemotaxis adherence degranulation of lysosomal enzymes and a retarded bacteric dal ab lity (6 7) Th s impa rment of migrat on may in some patients be reverted with drugs such as ascor bic acid increasing e g the intracellular levels of cGMP (6 7 13) In contrast to what has been found in Chediak Higashi s d sease our pat ents d d not show any defects in other functions than stimulated migration Furthermore neutroph ls showing ab normally short d stances m grated by the leading front cells were not enhanced more by ascorbic acid than the normally migrating neutrophils from pa tients and controls It could hence be argued that these defects do not seem to be due to mechanisms responsible for the defective assembly of mi crotubules as in patients with Chediak Higashi s disease where orientation of m grating neutrophils seems not to have been measured

In contrast to cases with small numbers of mi crotubules in the neutrophils and poor migratory capacity Gall n et al (14) described a 7 year-old patient with markedly increased number of cen triole associated microtubules in the migrating neutrophils and a defect ve cell locomotion together with delayed bactericidal act low adherence Thus abnormally low va var ous neutrophil functions may be associ too few as well as too many microtubules

The assay employed here for measure neutrophil locomot on is principally s m lar described by Nelson et al (20) Repo (28) and Ward (21) We have also analyzed the tion of the neutrophils in the cytotax n under the agarose—an additional informat is easily obtainable in the same assay as th variables (33) It is interest ng that the or ent migrat ng neutroph ls was sign f cantly lowe tients with ICS than in controls Centriol m crotubules have been suggested to be imp for cell orientation during locomotion (4 1 agents affecting microtubules such as v nbl and colchicine have been shown to decrea orientation (18 Palmblad et al unpubl shed vat ons) Whether th s abnormally low orien seen in all our patients is related to the num m crotubules some defects in the orientation centrioles or some other structural defect known

For the st mulat on of neutroph l locomot have used two different cytotax ns w th dif results in some patients The nature of these d ences is not known they may be rela ed to neutroph l surface receptors S nce the ne surface is equ pped with receptors for C5a f

ated compounds generated in serum in contact th agarose) and synthetic tripept des (5) (similar BF) it s conceivable that the neutroph ls could g ate d fferently after st mulation of these receptors due to its actual sens tivity It has recently been mon trated that defect ve neutroph l locomot on ght be found after stimulat on with one cytotax n hereas it s normal after act vat on with another 37) These f nd ngs emphas ze the importance study n neutroph ls with several d fferent motact c factors Also methods d st nguish ng cause of a defect ve locomotory response are eded to f nd out whether there is a pr mary defi ncy of the locomotor structures or whether the ects are secondary to other condit ons lead ng to act vat on of the cells We could not find any ns suggesting that recent infect ons would have n the cause of impa red neutrophil m grat on in pat ents Only little is however known about orn errors in the systems of cell locomotion

he analyses of the degree of or entation of cells a grad ent is an assay wh ch might be employed hed l ght on mechan sms which are suggested depend on m crotubules

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REFERENCES

Afzel us B A A human syndrome caused by im mot le c l a Sc ence 193 317 1976

— The mmot le c l a synd ome and other c l ary d s eases Int Rev Exp Pa hol 19 1 1979

Afzel us B A & El asson R Flagellae mutants n man on the heterogene ty of the immotile c l a syn drome J Ul rastruct Res 69 43 1979

Albrecht Buehler G & Bushnell A The orientat on of centrioles n m grat ng 3T3 cells Exp Cell Res 1 0 111 1979

Aswan kumar S Corcoran B Sch ffman E Day A R Freer R J Showell H J Becker E L & Pert C B Demonstra on of a receptor on rabb t neu roph ls for chemotact c pept des B ochem B ophys Res Commun 74 810 1977

Boxer L A Allen J M Watanabe A M Besch H R & Baehner R L Role of m crotubules in granulocyte adherence Blood 51 1045 1978

Boxer L A Wa anake A M R ster M Besch H R Al en J & Baehner R L Correct on of leukocyte funct on n Ched ak H gashi syndrome by ascor ba e N Engl J Med 296 1041 1976

8 Boxer L A Yoder M Bons b S Schm dt H Ho P Jers ld R & Baehner R L Effect of a chemotact c factor N formyl meth onyl pept de on adherence superox de an on generat on phagocyto sis and m crotubule assembly of human PMN leukocytes J Lab Cl n Med 93 506 1979

9 Caleb M Lecks H South M A & Norman M E Letter to the ed tor N Engl J Med 297 1012 1977

10 Chenoweth D E & Hugl T E Demonstrat on of a spec f c C5a receptor in intact human PMN leukocytes Proc Natl Acad Sc USA 75 3943 1978

11 El asson R Mossberg B Camner P & Afzel us B A The mmot le-cil a syndrome A congen tal c l ary abnormal ty as an et olog cal factor in chron c a rway nfect ons and male ste l ty N Engl J Med 297 1 1977

12 Ewetz L Palmblad J & Thore A The relat on sh p between lum nol chemolum nescence and k ll ng of Staph aureus during phagocytos s Proc Int Symp B olum nescence and Chemolum nescence Bruxelles 582 1979

13 Gall n J I El n R J Hubert R I Fau i A S Kal ner M A & Wolff S M Eff cacy of ascorb c ac d n Ched ak H ga h syndrome Blood 53 226 1979

14 Gall n J I Malech H L Wright D G Wh shnant J K & K rkpatri k C H Recurrent severe infect ons in a ch ld w th abnormal leukocyte funct on Poss ble relationsh p to n reased m crotubule assembly Blood 51 919 1978

15 Issekutz A C & B ggar W D Neutroph l che motax s in two pat ents w th recurrent staphylococcal sk n infect ons and hyper mmunoglobul n E J Lab Cl n Med 92 640 1978

16 Lup n A J & M sko G J Kartagener s synd ome w th abnormal t es of c l a J Otolaryngol 7 95 1978

17 MacGregor R R Spagnuolo P J & Lentnek A L Inh b t on of granulocyte adherence by ethanol pred n sone and asp rine measured w th an assay system N Engl J Med 91 642 1974

18 Malech H L Root R K & Gall n J I Structural analys s of human neutroph l m grat on Centriole m crotubule and m crof lament or entat on and func t on during chemotax s J Cell B ol 75 666 1977

19 Mossberg B Afzel us B A El asson R & Camner P On the pathogenes s of obstruct e lung d sease Scand J Resp r D s 59 55 1978

20 Nelson R D Qu e P G & S mmons R L Chemotax s under agarose J Immunol 115 1650 1975

21 Orr W & Ward P A Quant tat on of leukotax s in agarose by three d fferent methods J Immunol Methods 20 95 1978

22 Palmblad J Fast ng n man Effect on PMN granulocyte funct ons plasma ron and serum transferrin Scand J Haematol 17 217 1976

23 Palmblad J & Engstedt L Act at on of the bac ter c dal capac ty of blood granulocytes—evaluat on of a new method and the effect of levam sole Acta Pathol M crob ol Scand (C) 87 357 1979

24 Palmblad J Hallberg D & Rossner S Obes ty

plasma lipids and PMN granulocyte functions Scand J Haematol 19 293 a 1977
25 Payne C M & Glasser L The effects of steroids on peripheral blood lymphocytes containing parallel tubular arrays Am J Pathol 92 611 1978
26 Payne C M Jones J F Sieber D F & Fulginiti V A Parallel tubular arrays in severe combined immunodeficiency disease An ultrastructural study of peripheral blood lymphocytes Blood 50 55 1977
27 Pedersen H & Mygind N Absence of axonemal arms in nasal mucosa cilia in Kartagener's syndrome Nature 262 494 1976
28 Repo H Leukocyte migration agarose test for the assessment of human neutrophil chemotaxis Scand J Immunol 6 203 1977
29 Satir P Basis of flagellar motility in spermatozoa Current status In The spermatozoon (ed D Fawcett and J M Bedford) p 81 Urban Schwarzenberg Baltimore and Munich 1979
30 Stebbings H & Hyams J S Cell mo Longman London 1979
31 Sturgess J M Chao J Wong J Aspin N Turner J A P Cilia with defective radial spokes Engl J Med 300 53 1979
32 Uden A M Palmblad J Trang L & Venizelos N Effect of total fasting in patients with rheuma arthritis—clinical performance and neutrophil functions Int Symp Infect Immunocompromised Ho abstract p 55 Veldhofen 1980
33 Venizelos N Palmblad J & Uden A Methodological aspects of migration of granulo under agarose Acta Med Soc Suec 88 167 1979

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ffect of Long-Term Treatment with Human Leukocyte Interferon on Various Laboratory Parameters

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TRACT Leukocyte interferon was given by i m tion as adjuvant therapy to 9 patients with osrcoma The dose was 3×10^6 standard units daily ne month, and then 3 times a week for the next onths Blood samples were drawn at intervals number of routine tests during the 18-month se of interferon administration and during the equent 18 months On withdrawal of the inter treatment the mean Hb concentration rose ficantly and the mean ESR fell significantly e was no significant change in the leukocyte and let counts or in the alkaline phosphatase, alanine aspartate aminotransferase or plasma protein s

words interferon blood chemistry
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genous human leukocyte interferon has been l during the 70s at the Karolinska Hospital for tment of a number of tumour diseases (13 14) e Dec 1971 a clinical trial has been conducted hich patients with osteosarcoma have received rferon as an adjuvant form of treatment (13) r a period of 6 years 9 patients had completed 18 month course of interferon therapy and were owed for a further 18 months To ascertain the ty of long term interferon therapy clinical minations (6) of these patients were supnented with regular laboratory tests At the nning of this therapy all the patients were suf ng from an untreated tumour disease As the ables under examination might be influenced by tumour disease and the treatment of it—es ally surgery and blood transfusions—the study s confined to periods during and after interferon course when the effect of such factors appeared to be least marked

STUDY POPULATION AND METHODS

Patient series The 9 patients studied had osteosarcoma for which they had been receiving interferon as an ad juvant to conventional tumour treatment They had no history of disease prior to the development of osteosar coma At the beginning of the course of treatment the patients (6 males and 3 females) ranged in age from 10 to 28 years The intended primary treatment of the tumour was radical operation preceded in 6 cases by ra diotherapy The times for these measures and the time or replacement of concentrated interferon given initially by more purified preparations are given in Fig 1 The preoperative radiotherapy was given as cobolt-60 ir radiation The treatment schedule was 2 Gy daily (tumour dose) 5 days a week for 4 weeks by which time a total tumour dose of 40 Gy had been administered After an interval of 2 weeks 3 of these patients were given a further 24–28 Gy (tumour dose) following the same frac tionation schedule

Interferon preparations The interferon was produced by in vitro stimulation of blood bank leukocytes with Sendai virus (2 11) The course was started immediately after the diagnosis had been verified and thus before any other treatment for the tumour disease had been given The interferon was administered as an i m injection of 3×10^6 standard units daily for the first month and thereaf ter 3 times a week for a further 17 months This dose of interferon yields levels of 20–30 U/ml plasma (3) The treatment was started with concentrated interferon (2 11) and if troublesome side-effects occurred (6) it was re placed by a more purified preparation (2 11) The concentrated interferon contains $1–2\times10^6$ standard U/ml and its specific activity is $1–5\times10^4$ standard U/mg protein Purified interferon contains $5–20\times10^6$ standard U/ml and $1–5\times10^5$ standard U/mg protein

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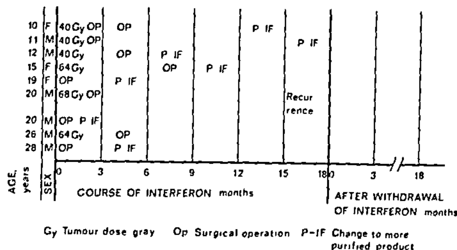


Fig 1 Time of in
therapy in relatio
forms of treatmen
change to more p
interferon

All 9 patients underwent regular clinical examinations and comprehensive laboratory tests During the interferon therapy they were checked 12–17 times During the following 18 months each patient was examined 5–12 times

Two patients developed local recurrence one of them in the last month of the interferon therapy and the other 2 years after the course had been completed As the test results for these 2 patients did not differ noticeably from those for the other patients they were not excluded from the series

Laboratory tests All analyses were performed at the routine laboratories of Karolinska Hospital The test methods used and the reference values of the blood variables are given in Table I

Statistical analysis The 18-month course of interferon treatment and the subsequent period of the same length were divided into 3 month periods for each of which the mean values of the respective variables were calculated for the individual patients Every effort was made to compare steady state Thus—in order to avoid the influence of the tumour burden radiotherapy operation and any blood transfusion etc during the initial course of the disease—the statistical analysis was confined to the last 9 months of the interferon therapy To avoid any unreliable of the interferon therapy the first 3 months afte were disregarded The mean values for the thre periods of interferon therapy were compared in with the respective values for the three post month periods A difference was regarded as sig $p<0.01$ The aggregate results of the laborator formed over the 3 year period are presented gra Fig 2 *a* *b* and *c*

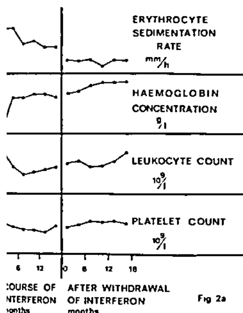
RESULTS

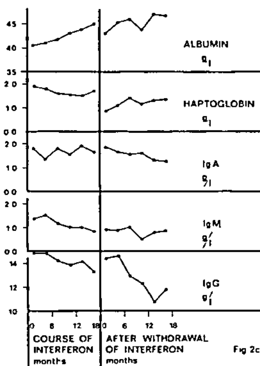
A significant difference between the va corded during and after the interferon ther found only for ESR and Hb concentration

Erythrocyte sedimentation rate The va the last 9 months of the interferon thera significantly higher than those for the per months after withdrawal of interferon (*p* Over the whole period of interferon treatme was a considerable drop in the ESR afte

Table I *Laboratory methods*

Parameter	Method	Reference value (ad
ESR (mm/h)	Routine method (modified from Westergren)	Men 1–15 women 1
Hb (g/l)	Routine method cyanmethaemoglobin	Men 140–170 wom 150
Leukocytes ($\times 10^9$/l)	Routine method manual	4 0–9 0
Platelets ($\times 10^9$/l)	Routine method manual	150–400
Electrophoresis	Agarose gel (Laurell ref 8)	
Albumin (g/l)	Immunological technique (turbidometry)	37–52
Haptoglobin (g/l)	Immunological technique (turbidometry)	0 4–2 5
IgG (g/l)	Immunological technique (turbidometry)	7 0–15 0
IgA (g/l)	Immunological technique electroimmunoassay	0 8–3 8
IgM (g/l)	Immunological technique electroimmunoassay	0 4–2 0
ASAT (μkat/l)	According to Scand Enzyme Comm (ref 12)	<0 70
ALAT (μkat/l)	According to Scand Enzyme Comm (ref 12)	<0 70
ALP (μkat/l)	According to Scand Enzyme Comm (ref 12)	0 8–4 0





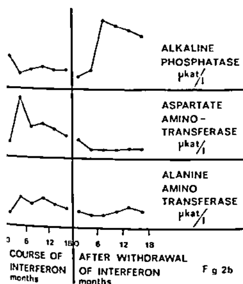


Fig 2 Course of the blood variables during and after interferon therapy O = mean of the single determination made in each of the 9 patients before interferon therapy ● = mean of the 9 means (each of several determinations in one patient) for the 3 month period

l of interferon there was a further decrease ed by a fairly steady state (Fig 2 *a*)

moglobin concentration The Hb level rose y to a plateau at the beginning of the inter treatment and remained fairly constant ghout the course (Fig 2 *a*) On withdrawal of rug there was a further increase to a new u The difference between the mean values for riods during and after treatment was statis significant ($p<0.01$)

locyte count There was no significant dif e between the counts for the 9 month periods Mean counts of about $5–6\times10^9$ cells/l were recorded for the 18 months of interferon therapy and the subsequent 18 months (Fig 2*a*)

Platelet count remained practically constant at $200–300\times10^9$ platelets/l throughout the 3 year period (Fig 2*a*)

Alkaline phosphatase In 6 of the patients the difference between the values during and after the therapy was small In the other 3 patients aged 10 11 and 12 years a high level was recorded during the interferon treatment and a steep increase after withdrawal of the drug The high levels recorded in

these 3 patients rule out a meaningful statistical analysis (Fig 2 *b*)

Alanine and aspartate aminotransferase There was no significant change in the levels of these enzymes on discontinuing the interferon therapy (Fig 2 *b*)

Plasma proteins The analysis of the plasma proteins by electrophoresis disclosed no evidence of a significant change when discontinuing the interferon therapy (Fig 2 *c*)

DISCUSSION

Interferon has been increasingly applied in clinical treatment Administered in i m injections it has been used in cases of virus infections and malignant diseases The ESR has been reported to be higher during interferon therapy (4 14) Bone marrow suppression with low granulocyte platelet and reticulocyte counts has been noted in some studies (5 9 10) but not in others (1 4 7) It has been suggested that the suppression is dose-dependent (5 9) An elevated transaminase activity during interferon therapy has been reported in patients with hepatitis malignant disease involving the liver and congenital virus infections (1 5 7) The interval between injections the dose and the duration of the therapy in these studies have varied widely The treatment has often been introduced in an aggressive stage of the disease In addition some of the patients had recently undergone radiotherapy for underlying malignant disease and it is therefore difficult to judge whether any trends disclosed by the laboratory tests should be ascribed to the interferon therapy alone

Despite the small number of subjects in this study the long follow-up time with relatively frequent sampling enables trends in the material to be analysed in relation to the interferon therapy The study was largely confined to periods during the treatment when influence of other factors would seem to be least marked As each patient served as his own control the skew age and sex distribution may be disregarded and no control group is required

The implications of the observed significant difference in ESR over the relevant intervals are unclear since there was a steady decrease in ESR from the time of initiation of the treatment We thus cannot be sure that posttherapy reduction was solely due to the withdrawal of the interferon (Fig 2 *a*) Whether this trend is ascribed to a change over to the more purified interferon is als to say since this was made at different ti course of the treatment (Fig 1)

During the first 3 months of the cours feron the Hb concentration rose to a pl after withdrawal of the drug there was a f to a new plateau The differences be mean values for the compared 3 month pe ing and after the therapy were statist nificant

As regards the alkaline phosphatase mean for the 9 patients increased after feron therapy had been discontinued (Fi the other hand the individual difference periods in question were not statistically s The high alkaline phosphatase level both after interferon therapy is accounted for l of the patients aged 10 11 and 12 yea the last 9 months of the treatment the mea these patients was 8 4 against 13 5 µka first 9 months after withdrawal of the dru

There was no significant difference be mean values of ASAT and ALAT befor withdrawal of the drug Nor was there a in the leukocyte and platelet counts thro follow up period

In spite of the significantly elevated I during the interferon treatment there wa tically significant change in the level of pl teins Throughout the follow up period was high in relation to age while the Ig the low side The IgG fell during the cou treatment but when the drug was withdra was a transient increase

Taken together long term treatment sarcoma patients with human leukocyte i in the dose used did not affect mark biochemical variables examined Likev severe symptomatic side effects were enc (6) In studies on patients with other receiving higher doses of interferon u therapy was found to exert an effect on blood components There is a clear need t the investigation of the effect of interferon diseases and to examine the early phase interference from other factors

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REFERENCES

Arvin A M Yeager A S & Merigan T C Effects of leukocyte interferon on urinary excretion of cytomegalo virus by infants J Infect Dis (Suppl) 133 A205–A210 1976

Cantell K Hirvonen S Mogensen K E & Pyhala L Human leukocyte interferon production purification stability and animal experiments In The production and use of interferon for the treatment and prevention of human virus infections In vitro monograph vol 3 (ed C Waymouth) pp 33–38 Tissue Culture Association Rockville 1974

Cantell K & Pyhala L Pharmacokinetics of human leukocyte interferon In Antivirals with clinical potential (ed T C Merigan) pp 6–12 University of Chicago Press Chicago and London 1976

Emodi G Rufli T Just M & Hernandez R Human interferon therapy for herpes zoster in adults Scand J Infect Dis 7 1–5 1975

Greenberg H B Pollard R B Lutwick L I Gregory R B Robinson W S & Merigan T C Human leukocyte interferon and hepatitis B virus infection N Engl J Med 295 517–520 1976

Ingimarsson S Cantell K & Strander H Symptomatic side effects of long term treatment with human leukocyte interferon J Infect Dis In press 1980

Jordan G W Fried P & Merigan T C Administration of human leukocyte interferon in herpes zoster I Safety circulating antiviral activity and host responses to infection J Infect Dis 130 56–62 1974

8 Laurell C B (ed) Electrophoretic and electro-immunochemical analysis of proteins Scand J Clin Lab Invest (Suppl) 124 1972

9 Merigan T C Pharmacokinetics and side effects of interferon in man Tex Rep Biol Med 35 541–547 1977

10 Merigan T C Rand K H Pollard R B Abdallah P S Jordan G W & Fried R P Human leukocyte interferon for the treatment of herpes zoster in patients with cancer N Engl J Med 298 981–987 1978

11 Mogensen K E & Cantell K Production and preparation of human leukocyte interferon Pharmacol Ther (C) 1 369–381 1977

12 Scand Enzyme Comm Recommended methods for determination of four encymes in blood Scand J Clin Lab Invest 33 291–306 1974

13 Strander H Cantell K Ingimarsson S Jakobsson P Å Nilsonne U & Soderberg G Interferon treatment of osteogenic sarcoma A clinical trial Conference on modulation of host immune resistance in the prevention or treatment of induced neoplasias Dec 9–11 1974 Fogarty Int Center Proc US Government Printing Office Washington DC 28 377–381 1977

14 Strander H Jakobsson P Å Carlstrom G & Cantell K Administration of potent interferon to patients with malignant diseases Cancer Cytol 13 18–19 1973

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Immunological Studies on Human Thymus

Occ rre ce a I D str l t i f I glob l s a id I n log cal Receptors i i Mys stl en Gra s a l Control Pat ents

B rger Christensson Georg Matell and Peter B berfeld

n e D pu ent f Pa l log Ka l ska In et the Depa n e t of Imm nolog Nat onal Bacter olog c l Labo a ors and tl e Dep t nen of Med c ne S dersj kl set St kl olm S eden

TRACT Suspended cells and tissue sect ons i myasthen a gravis (MG) and control thymuses characterized for surface expression and his-ical distribut on of immunoglobul n (Ig) and re ors for sheep erythrocytes (SE) the Fc part of (Fcγ) and of IgM (Fcμ) and complement factors and C3d (CR) In sect ons the cortical areas i both MG and control thymuses expressed SE as as Fcγ receptors whereas medullary areas only red weak SE binding In contrast to control pa s MG thymuses also contained Ig+ cells con l to nodular areas of the thymic medulla These les stained for both IgG and IgM and were lonal w th respect to light chains In several i IgD was found as well In add tion the nodular s were pos tive for C3b and C3d receptors In l sect ons these Ig+ CR+ nodules corresponded orpholog cally characterist c lymphoid follicles i B cell follicles were observed in variable num in all MG thymuses whether hyperplast c or normal histology Five thymomas gave rogeneous results with regard to immunological kers Comparison of methods showed that recep ind Ig ind cation on sections was more sensitive correspond ng tests on thymus cells in suspen

wo d human thymus myasthen a grav s m olog cal ma kers mmunoglobul n complement re ors

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ut 75% of pat ents with myasthen a gravis i) have hyperplast c thymuses with foll cular structures and about 10% have thymomas (7) olog cal observat ons and mmunofluorescence les of cells recovered from myasthen c muses (1 2 9 11 15) have suggested an abnor B cell prol feration n MG thymuses There is also evidence for both humoral (16) and cell mediated (10 17 19) auto mmune reactiv ty in MG Ho ever the relevance of the thym c changes in the pathogenesis of MG is far from clear although suggested by the benef cial effect of thymectomy (18)

In the present study the correlation between h s tological changes and the presence and t ssue d s tribut on of T and B cell markers was invest gated and compared with that of thymuses from control subjects

MATERIAL AND METHODS

Thymus b ops es from ? thymectom zed MG pat ents and from 13 pat ents undergo ng open cardiac surgery (con trols) were stud ed The b ops es were d v ded and p eces for mmunolog cal s ud es were qu ck frozen n stream ng CO The frozen t ssues were kept n 70°C unt l they were cryosect oned n 5–10 μ th ck sect ons The sect ons were transferred to co ersl ps and allowed to dry n room temperatu e for one hour In some experiments thymus spec mens were also resuspended and v able cells were tested Morphology was exam ned n con ent onal h tolog cal preparat ons

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Abb e at ons MG mya hen a gra s SE heep erythrocytes Ig immunoglobul n AET am no-ethyl th oron um brom de hydrobrom de PBS = phos phate buffered sal ne IFL mmunofluorescence PAP = mmunoperox dase OEAG ox erythrocytes coa ed w th ant body of the IgG class OEAM ox erythrocy es coa ed w th ant body of the IgM class OEAMc ox erythrocytes coated w th ant body of the IgM class and complement factor C3b complement factor C3b C3d complement factor C3d Cr complement recep or Fcγ receptor for the Fc part of the IgG molecule Fcμ receptor for the Fc part of the IgM molecule FITC fluoresce n soth ocyana e F(ab)² an Ig molecule lack ng the Fc fragment C5 complement factor C5 C6 complement factor C6 FCS fetal calf serum OE ox erythrocyte ALP alkal ne phosphatase ACP ac d phosphatase NSE non spec f c esterase



F g I Frozen sect on of control thymus showing dense b nd ng of AET treated sheep erythrocytes over cortical areas but only sparse b nd ng over medullary areas

I d ator systems

Receptors for sheep erythrocytes (SE) were demonstrated w th SE treated w th AET (2 am no-ethylthiouron um brom de hydrobromide S gma) accord ng to Kaplan and Clark (14) In short one volume of packed SE were in c bated w th four volumes of 0 143 *M* AET d ssolved n de onised water at pH 9 for 15 m n at 37°C washed five t mes in phosphate buffered sal ne (PBS) and resuspended to 1% in PBS w th 0 1% gelat n

For demonstrat on of Fcγ and Fcμ receptors ox eryth rocytes (OE) were incubated w th subagglut nat ng doses of anti OE IgG and IgM respectively for 30 m n at 37°C The result ng OEAG and OEAM nd cator cells were washed three t mes in PBS and resuspended to 0 5% in PBS gelat n as previously descr bed n deta l (8)

For demonstrat on of C3d receptors OEAM were coated w th C3d by ncubat on w th a C5 def c ent mouse serum d luted 1 2 at 37°C for 15 m n For demonstration of C3b receptors C6 def cient rabb t serum was used The EAMC nd cator cells were subsequently washed three t mes and resuspended to 0 5% in PBS gelat n The gela t n conta n ng buffer was shown to d m nish unspec f c b nd ng (8)

Receptor nd cat on

Suspended cells were ncubated w th respect ve ind cator erythrocyte system accord ng to convent onal techn ques (1?) For concom tant double nd cation of SE and Fcγ receptors e ther ind cator system was labelled w th fluoresce n soth ocyanate (FITC)

The frozen t ssue sections were incubated accord ng to the closed chamber techn que of Tønder et al (26) In short *the concav ty of a m croculture sl de was f lled with* ind cator cells a coversl p was adapted over the cav ty with the ect on on the ins de and the glass sl des were then pressed together mak ng a closed chamber conta n ng both the sect on and the nd cator erythrocytes Incuba t on w th the coversl p down for 30 m n allowed the nd cator cells to sediment on and b nd to the receptors After *ncubation the chamber was turned coversl p up* and erythrocytes not adher ng to the sect on were allowed to settle for 15 m n Subsequently the sect ons v amined under m croscope and the dens ty and p d stribut on of the adsorbed ind cator erythroc determ ned The dens ty was evaluated from and the d stribut on pattern denoted as medullar cal and as nodular or d ffuse For photography t ons were f xed n 3% glutaraldehyde and stai benz d ne and tolu d ne blue for easy differen erythrocytes and thymus t ssue

I nn nofl orescent (IFL) st n ng

Unf xed cryosect ons were incubated in PBS co 5% fetal calf serum (FCS) prior to ncuba on w sera Appropriate d lut ons of ant sera aga n t h classes and l ght chains were used FITC-co F(ab) fragments of ant IgM ant IgD an Ig and ant λ were purchased from Kallestads Labo Ant IgG FITC F(ab) fragments were ob a n the Nat onal Bacteriolog cal Laboratory Stockho sect ons were ncubated w th ant body at ro perature for one hour and washed n PBS FCS before mount ng n buffered glycerol T were exam ned in a Ze ss m croscope w th ep l u at ×100 and ×400 magn f cat on

Imm noperox dase (PAP) sta n ng

Deparaf n zed sect ons were consecut vely trea rabb t ant bod es aga nst human Ig classes goat serum and preformed rabb t ant perox dase pe (PAP) complexes accord ng to the techn que of S (?4) *Bound perox dase was demonstrated by* w th d aminobenz d ne

H stocl en s ry

Convent onal methods were used for sta n ng of cryosect ons for demonstrat on of alkal ne (ALP) phosphatase (ACP) (5) non spec f c esterase (N *perox dase (27)*

RESULTS

SE C3 a d Fc receptors

Eleven thymus biopsies from pat ents unde cardiac surgery (control thymuses) were gated for SE Fcγ Fcμ C3d and C3b recept all cases receptors for SE could be demons frozen thymus sect ons us ng untreated SE b bind ng was stronger and the adsorpt on when AET treated SE were used The ads was dense in cortical areas and only sparse medullary regions (Fig *I*) *Cortical areas* vealed a dense b nd ng of OEAG but v rtu bind ng was found n the medulla Untrea AET treated OE on the other hand d d not the thymus sections The cortical b nd ng of AET and OEAG was on ser al sect ons we cover the same areas All *control thymu es*

le I *Receptor d str b t n cr sect ts f n s b ops es fro c trol s bj cts c I MG pa t w I tl t I perpl is a r n r af (n ted) I stolog*

Diffu e recep or d stribut on c cort al recep or bu on n nodular receptor d stribut on n the u a

no	Age (y)	Sex	SE AET	Fcγ	C3d
r ol					
	7	♂	+++c	+ c	
r	1?	♀	+++c	++c	
	7	♀	+++c	+++c	
	7	♀	+++c	+++c	
	?	♀	+++c	++c	
	9	♀	+++c	++c	
	7	♂	+++c	++c	
3	5	♀	+++c	+++c	
	3	♀	+++c	+++c	
	8	♂	+++c	++c	
	6	♀	+++c	+++c	
oma					
	63	♂	+++d	+++d	
	39	♀	++d	+d	
	55	♀		++d	+++d
	0	♂	+c	++c	+++n
	37	♀	+++d	+++d	
la *q e*?*p as a*					
	34	♀	+++c	++c	++n
	?	♀	+++c	+ c	++n
	?3	♀	+++c	++c	+ n
	3	♀	+++c	++c	+++n
		♀	+++c	+c	+++n
	9	♂	++c		+ n
	6	o	+c	++c	+++n
	?7	♀	++c	++c	++n
	35	♀	+++c	++c	+++n
	31	♀	++c	+++c	+ n
	0	♀	+++c	++c	+++n
	3	♀	+++c	++c	+ n
	3	♀	++c	++c	++n
nal h s olog					
	55	♀	+++c	+++c	+++n
	44	♀	++c	+c	+ n
	55	♀	+++c	+++c	++n
	30	♀	+c	+++c	+++n

hough cl n cally a relaps ng thymoma no morpho al y clear thymoma ous t ssue was found

s aged 3–1? years mean 6 9) had s m lar d s t on patterns for these receptors (Table I) her the cortex nor the medulla of these nuses showed receptors for Fcμ C3d or C3b ne thymus b ops es from MG pat ents were ped accord ng to h stopathology in 5 cases with ioma (aged 30–63 mean 43) 13 w th follicular



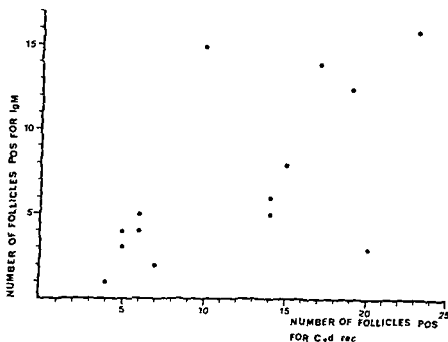
F g ? MG thymus show ng a strong b nd ng of C3-coated ox erythrocytes over nodular areas n the thym c medulla

hyperplas a (aged ?0–35 mean ?6) and 4 w th normal involuted morphology w thout s gns of hyperplasia or thymoma (aged 30–55 mean 36)

In three of the five thymoma cases there was a *d ffuse overlapp ng d stribut on of receptors* for both SE and Fcγ but no C3 receptors One case had no SE receptors but a d ffuse o erlapp ng distribution of both Fcγ and C3d receptors One case (no 15) although cl n cally and rad olog cally a relaps ng thymoma had morpholog cally only areas *of follicular hyperplasia* and showed a receptor n d cation pattern characteristic of th s k nd of thymus morphology (see below) with cort cal SE receptors and medullary nodules pos t ve for C3d receptors (Table I)

All 13 myasthen c pat ents w th foll ular hy*perplasia had* receptors for SE AET n the cortical areas Twelve of these cases also had a moderately strong Fcγ receptor activity overlapp ng with *SE receptors in the cortex s m lar to that seen in* the controls In contrast to the find ngs in control thymuses these MG thymuses had C3 receptors w th n nodular areas in the medulla (Fig ?) Th s was seen in all these cases but the number of posi t ve nodules varied w th n w de ranges

In four myasthen c pat ents the thymus morphology appeared essent ally normal or atroph c without signs of foll cular hyperplasia or thymoma Although there was no histolog cally ev dent foll cular hyperplas a these cases in add t on to cort cal SE and Fcγ receptors also had nodular C3 receptor act vity in the thym c medulla (Table I) qu te s m lar to the receptor distribut on pattern seen n cases with foll cular medullary hyperplas a



F g 3 Rela on betw number of foll cles for IgM by mmunofl cence and he numbe l cles po e fo C3 tors as compared on frozen sect ons

The C3 receptor pos tive nodules in the thym c medulla of myasthen c patients were sho vn to be pos tive both for C3d and C3b receptors but to lack receptors for Fcγ Fcμ and SE In several cases the number of C3 receptor pos t ve areas out numbered the foll cular areas detectable by morphology alone on serial sect ons None of the myasthen c thymuses d d b nd OEAM ind cator cells

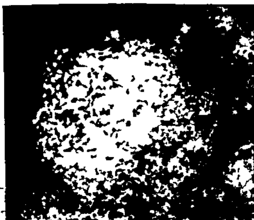
As expected around 90% of the thym s cells in suspens on of e ther control or MG thymuses formed E rosettes however relatively few cells formed Fcγ rosettes (Table II) This was also the case for Ig and C3d receptors (Table II) There was no statist cally signif ant differences bet veen the hyperplastic thymoma or control groups with re gard to any of the markers stud ed (Table II) Only a few SE+ cells also expressed Fcγ receptors as ind cated by concom tant double ind cation experi ments

I ofl oresce ce

To further characterize the subpopulat on of ... lary cells n myasthen c thymuses posit ... receptors d rect IFL stud es were perform... sect ons serial to those used for C3 recep ... m nat on Th rteen hyperplastic MG th ... w thout thymoma and six control cases were ... tigated By direct IFL on the cryostate sect... the MG thymuses revealed Ig+ nodular areas in the medulla None of the control thymu... posit ve The same nodular areas could be ... tif ed as pos tive both for C3 receptor act ... for Ig A correlation was found between the ... of areas positive for C3 receptors and Ig ... sect ons (Fig 3) In general more C3 recep... t ve areas were found than areas pos t ... W th monospec fic antisera the Ig+ area... shown to conta n both IgG and IgM as well a... λ cha ns Nodules pos t ve for IgD were also ... in several case The IgM stain ng was ...

Table II *S rface olog l arkers res spe ded tl s cells*

No of pats	Diagno s	Percentage of cells w th receptors for (mean and range)				
		SE AET	Fcγ	Fcμ	C3	Ig
13	Control	90 (8? 99)	? 4 (0–7)	<1	? 8 (0–11)	9 0-
1?	MG foll cular h perplasia normal morphology	91 9 (8 97)	3 4 (0–9	<1	5 3 0–16)	3 8 0-
6	MG thymoma	88 3 (79–97)	9 (? 0)	<1	3 5 (1 14	6 8 0-



4 MG thymus showing staining for IgM in nodular ... of the thymic medulla Note the lace like mem... associated staining pattern and the more coarse ...lar staining of central areas

...ment in the central part of the nodules but ...ker in the periphery whereas IgD predominant ...ained the mantle zone of the nodules Some ... in addition a few cells centrally located in ...e odules were also IgD+ (Fig 4)

...unoperoxidase staining

...results of PAP staining corroborated in general ...the observations made by IFL and clearly evi... ...ed the localization of Ig to cells of the nodular ...

...ochemistry

...medullary nodules did not stain for ALP ACP ...or peroxidase Outside these areas there was ...lly a weak reaction for both ACP and NSE ...in the medulla and a moderately positive reac... in the cortex Only endothelial cells in capil... ...s and some reticular cells in follicles were posi... for ALP Peroxidase activity was usually found ...few reticular cells within the medullary ...les and in some cells associated with lobular ...as The latter cells were mostly identified as ...ulocyte like cells

DISCUSSION

...ious characterization of thymocytes with re... ...l to immunological markers have mainly been ...ved from studies on resuspended thymus cells These studies have shown that the majority of thymocytes can bind SE but that some thymocytes do not (12)

By IFL usually less than 1% of the thymus cells are Ig+ However in MG an increased but varying number of Ig+ cells has been reported (Table III) Similar results were obtained in the present study with regard to SE+ and Ig+ cells in resuspended normal thymuses (Table III) In this study of MG thymuses we also observed an increased but variable percentage of Fcγ receptor positive cells In addition the MG thymuses also contained variable numbers of cells with complement receptors From Table III it is evident that the quantification of Ig bearing thymus cells in suspension gives quite variable results both between different investigators and from case to case It seems that quantitative measurements on the frequency of B cells in resuspended MG thymuses might not be a very reliable method for the estimation of B cell activity

Our observations on the histological distribution of receptors in cryosections of thymus tissue indicated that the majority of SE+ cells reside in the cortical area in agreement with the histologically clear dominance of thymocytes in these areas The almost complete absence of SE binding in the medullary regions cannot be convincingly attributed to a lower concentration of thymocytes in these areas but is probably rather due to a lack of SE receptors with enough binding affinity to be demonstrated by the method used The idea that medullary thymocytes have SE receptors with a weaker affinity is also supported by the observations that among resuspended thymocytes subpopulations with high and low affinity for SE can be found as estimated both by the number of SE bound to the thymocytes as well as varying capacity of thymocytes to bind SE at 37°C (12) Furthermore T cell areas in frozen sections of peripheral lymphoid tissues show virtually no SE binding although most resuspended T cells from peripheral lymphoid tissues form SE rosettes at room temperature or 4 C These apparent differences in SE binding capacity between cortical and medullary thymocytes could reflect steps of thymocyte maturation within the thymus (13) In this respect medullary thymocytes seem to be more similar to peripheral T cells than cortical thymocytes

On resuspended thymus cells Fcγ receptors have previously been shown to occur on a small thymocyte population (20) Our observations on

Table III *Studies on the frequency of B and T cells in resuspended MG thymuses*

Reference	No of pats	Diagnosis	Percentage of cells with receptor for (mean and rang				
			SE	Fcγ	Fcμ	C3	Ig
Abdou et al (2)	4	MG	73			11	10
	4	Control	86			5	3
Shirai et al (22)	7	MG hyperplasia	89 (80–95)				5 (<0.5-
	2	Persistent thymoma	94 (92–97)				<0.5
	4	Control	95±3 4				<0.5
Birnbaum and Tsairis (6)	5	MG	59 5 (35 9–88 6)			1 1 (0 8–1 6)	
	1	Thymoma	49 3			1 5	
	4	Control	(48 8–59.5)			(1 1–2 9)	
Cook et al (11)	12	MG	92				3
	6	Control	96				1
Lisak et al (15)	18	MG	79±1 6				19±1
	6	Control	89±4.5				9
Aarli et al (1)	4	MG	90 (84–97)	7 (2–14)		17 (25 9)	<1
	2	Thymoma	91 (90 92)	5 5 (4 7)		14 (14 14)	15
	5	Control	86	6		6	<1
Present study	12	MG hyperplasia	91 9 (82–97)	3 4 (0–9)	<1	5 3 (6–16)	38 (0-
	6	Persistent thymoma	88 3 (79–97)	9 (2–20)	<1	3.5 (1–14)	61 (0-
	13	Control	90 (82–99)	2 4 (0–7)	<1	2 8 (0–11)	29 (0-

[a] Mean of two observations [b] One case tested [c] C3b [d] C3d

cryosections indicate an overlapping histological distribution of Fcγ and SE receptors in cortical areas but it was not possible to conclude whether these two receptors were located on the same or different cells However the absence of Fcγ indication in medullary regions of normal thymuses apparently excludes epithelial cells as having Fcγ receptors Furthermore the experiments with simultaneous indication for SE and EAG receptors on cells in suspension seem to indicate that these receptors are mostly present on different thymic cells Thus cells that are not easily brought into suspension i e stromal cells may account for most of the cortical expression of Fcγ receptors Alternatively these receptors are easier to indicate on sectioned thymic cells than on the surface of the resuspended cells

The absence of demonstrable Fcμ and C3 receptors in sections of normal thymuses is in agreement with observations on thymocytes in susp (Table II)

In contrast to others (1) we found no differ the SE receptor distribution pattern betwee and control thymuses The same pattern of distribution of SE and Fcγ receptors was f both in the (young) control group and in M tients Thus in this respect there are sim between MG thymuses and the premy thymus of childhood and adolescence

In the present study receptors for C3 were f in all myasthenic patients except three wh had thymomas All MG patients with f hyperplasia normal or involuted thymus phology had C3 receptors mostly coinciding nodular areas in the thymic medulla. The numb C3+ nodules varied considerably between the tients Also thymus biopsies without histolo distinct nodules revealed C3 receptor-po

ullary areas Thus C3 receptor demonstration
ore sensitive in revealing follicular/nodular
rplasia than conventional histopathology
milar observations of C3 receptors in follicular
s in MG thymuses have been reported
where (1 4 23) In agreement with Staber et al
we found OEAMC binding selectively to the
ullary follicles In the other reports also a dif
medullary binding was noted (1 4) These dif
it patterns could be due to technical variations
e present study bovine erythrocytes were used
dicator OEAG cells avoiding the binding of SE
E receptors Occurrence of Ig+ cells in MG
uses has been reported in several studies (Ta
I)

r morphological and immunologic findings (the
nce of C3 receptors and Ig) support the con
on that the nodular structures of the MG
ic medulla are follicular germinal centre equiv
s containing proliferating B lymphocytes The
ent distribution of IgM and IgD within these
ic follicles seems to reflect stages in the dif
tiation of proliferating B lymphocytes identical
at we have seen in peripheral lymphoid tissue
often numerous Ig+ and C3+ areas demon
e in sections of MG thymuses usually con
ed with the relatively few B cells found in sus
ons of the same MG thymuses This indicates
he histological techniques were more sensitive
ie demonstration of B cells than cell counting
ibly due to difficulties in resuspending the B
of the relatively cohesive follicular structures

examined only relatively few cases of
oma but some observations may have general
cations In all cases diffuse Fcγ receptor ac
was seen histologically In one case no SE
tors were found but a diffuse strong C3 recep-
ctivity suggesting that other lymphoid cells
thymocytes were associated with this thymo-
Thus our observations seem to indicate that
hymomas are heterogeneous with respect to
receptors tested for Since the examined
iomas were mixed proliferations of epithelial
lymphoid cells it was difficult to ascertain
h type of cell expressed respective receptor
ity Obviously a larger spectrum of thymomas
to be examined to further elucidate the im
ological phenotype of the associated lympho
s

he absence of B cell follicles and signs of Ig
luction within thymomatous tissue was a consistent finding This observation might be added to the clinical observations such as thymectomy response age and sex distribution as well as anti acetylcholine antibody titres suggesting that the thymoma cases are a disease entity somewhat different from other MG cases

In conclusion the present observations seem to indicate that high avidity SE+ thymocytes and OEAG+thymus cells are concentrated mainly with in the thymic cortex In contrast thymocytes in medullary regions probably have receptors with lower binding avidity for SE and OEAG if any

In agreement with other histochemical studies (25) the medullary follicles showed staining reactions similar to those of lymph nodes (21) and excluded the possibility of monocytes being the cells responsible for the observed CR+ and Ig+ reactions

In myasthenic thymuses nodular areas of the medulla corresponded to follicular B cell areas of peripheral lymphoid tissues in agreement with previous reports (1 23)

It is of interest from a diagnostic point of view to note that the histological demonstration of C3 receptors and Ig+ cells appeared to be more sensitive for demonstration of follicular areas in MG thymuses than conventional histopathology This might be of clinical importance since a low number of follicles has been suggested to correlate with a better postoperative prognosis (3)

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REFERENCES

1 Aarli J A Heimann P Matre R Thunold S & Tonder O Lymphocyte subpopulations in thymus and blood from patients with myasthenia gravis J Neurol Neurosurg Psychiatry 42 291 1979
2 Abdou N I Lisak R P Zweiman B Abrahamsohn I & Penn A S The thymus in myasthenia gravis Evidence for altered cell populations N Engl J Med 291 1271 1974
3 Alpert L I Papatestas A Kark A Osserman R S & Osserman K A histologic reappraisal of the thymus in myasthenia gravis A correlative study of thymic pathology and response to thymectomy Arch Pathol 91 55 1971
4 Arimori S Nakata Y Tada S Kobashi H Ichikawa Y & Koriyama K Studies on lympho-

cyte subpopulations and their responses to mitogenic stimulations of myasthenic patients Keio J Med 24 311 1975
5 Barka T & Andersson P J Histochemical method for acid phosphatase using pararosa aniline as coupler J Histochem Cytochem 19 294 1962
6 Birnbaum G & Tsairis P Thymic lymphocytes in myasthenia gravis Ann Neurol 1 331 1977
7 Castleman B The pathology of the thymus gland in myasthenia gravis Ann NY Acad Sci 135 496 1966
8 Christensson B & Biberfeld P Distribution of Fc and complement receptors in spleen sections I Comparison of various erythrocyte indicator systems J Immunol Methods 19 13 1978
9 Christensson B Biberfeld P & Matell G Immunological characteristics of subpopulations of thymic cells in myasthenia gravis Scand J Immunol 8 153 1978
10 Conti Tronconi B M Morgutti M Shgirlanzoni A & Clementi F Cellular immune response against acetylcholine receptor in myasthenia gravis I Relevance to clinical course and pathogenesis Neurology 29 496 1979
11 Cook J D Trotter J L Engel W K & McIntosh C L Altered immunologic cell populations in thymuses from myasthenia gravis patients Neurology 27 365 1977
12 Galili U & Schlesinger M Subpopulations of human thymus cells differing in their capacity to form stable E-rosettes and in their immunologic reactivity J Immunol 115 827 1978
13 Hopper K & Shortman K The differentiation of T lymphocytes III The behaviour of subpopulations of mouse thymus cells in short term cell culture Cell Immunol 27 256 1976
14 Kaplan M E & Clark C An improved rosetting assay for detection of human T lymphocytes J Immunol Methods 5 131 1974
15 Lisak R O Zweiman B & Phillips S M Thymic and peripheral blood T and B-cell levels in myasthenia gravis Neurology 28 1298 1978
16 Mittag T Kornfeld P Tormay A & Woo C Detection of anti acetylcholine receptor factors in serum and thymus from patients with myasthenia gravis N Engl J Med 294 691 1976
17 Morgutti M Conti Tronconi B M Sghirla[illegible] A & Clementi F Cellular immune respo[illegible] acetylcholine receptor in myasthenia gra[illegible] Thymectomy and corticosteroids Neurolog[illegible] 1979
18 Papatestas A E Alpert L I Osserman [illegible] Osserman R S & Kark A E Studies [illegible] thenia gravis Effects of thymectomy Result[illegible] patients with nonthymomatous and thymo[illegible] myasthenia gravis 1941–1969 Am J Med [illegible] 1971
19 Richman D P Patrick J & Arnason B [illegible] Cellular immunity in myasthenia gravis R[illegible] to purified acetylcholine receptor and a[illegible] thymocytes N Engl J Med 294 694 19[illegible]6
20 Samarut C Brocher J & Revillard J P [illegible] tion of cells binding erythrocyte antibody (E[illegible] plexes in human lymphoid populations Sca[illegible] munol 5 221 1976
21 Seymour G J Dockrell H M & Greenspa[illegible] Enzyme differentiation of lymphocyte subp[illegible] in sections of human lymph nodes fo[illegible] periodontal disease Clin Exp Immunol 3[illegible] 1[illegible]
22 Shirai T Miyata M Nakase A & Itoh T [illegible] phocyte subpopulation in neoplastic and non[illegible] tic thymus and in blood of patients with m[illegible] gravis Clin Exp Immunol 26 118 1976
23 Staber F G Fink U & Sack W B lymph[illegible] the thymus of patients with myasthenia grav[illegible] J Med 292 1032 1975
24 Sternberger L A Immunocytochemistr[illegible] tice Hall Englewood Cliffs New Jersey 197[illegible]
25 Tamaoki N Habu S & Kameya T Thy[illegible] phoid follicles in autoimmune diseases II H[illegible] cal histochemical and electron microscopic Keio J Med 20 57 1971
26 Tönder O Milgrom F & Witebsky E [illegible] agglutination with tissue sections J Exp [illegible] 265 1964
27 Yam L T Li C Y & Crosby W H [illegible] chemical identification of monocytes and [illegible] cytes Am J Clin Pathol 55 283 1970

High Immune Responsiveness in a Family :h Multiple Paraproteinaemia and Autoimmune Thyroid Disease

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RACT Immune responsiveness was investi in a family comprising 12 first and second e relatives one of whom had κ myelomatosis IgA λ paraproteinaemia two Graves disease a further two thyroid antibodies without se Relatives by marriage served as controls meters of immune capacity studied were the ral and cellular immune response to haemo- n of Helix pomatia (HPH) dinitrochloroben (DNCB) skin reactivity and in vitro lympho- proliferation capacity to phytohaemagglutinin) Mean antibody titres to HPH were higher in amily than in the control group in all main asses and IgG subclasses after primary and dary immunization, and the difference was tically significant for IgG IgG and IgG_4 titres could not have been predicted from the (normal) n Ig levels in this family In vitro lymphocyte feration capacity to HPH after primary and dary immunization was also significantly in sed DNCB skin reactivity also tended to be high he family whereas PHA induced lymphocyte feration was normal These findings support the that myelomatosis clusters in families with une dysregulation

words paraproteinaemia thyroid disease familial une response

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netic susceptibility to plasma cell dyscrasia is ested in humans by a higher incidence of iple myeloma (13 15 38) and macroglobulin ia (22) in relatives of patients with these ases than in the general population Some ies (13 22) but not all (26) have shown higher m Ig levels in these relatives than in control ulations and this might be interpreted as a lency towards dysregulation of immuno ulin (Ig) synthesis in these families Further as been shown that strains of mice with easy inducible plasma cell tumours have higher antibody responses than strains which do not develop plasma cell tumours (39)

Therefore we were interested in measuring the immune responsiveness in a family with para proteinaemia This was possible in all 10 living first and second-degree relatives of two brothers with κ myeloma and IgA paraproteinaemia respectively The humoral immune responsiveness to the primary antigen haemocyanin of Helix pomatia (HPH) (14 34) could be extensively measured by differentiating the antibody response in the IgM IgG IgA class specific and the four IgG subclass specific antibody titres to HPH after primary and secondary immunization (35) Cellular immune capacity was investigated by measuring in vitro lymphocyte proliferation capacity to HPH and to phytohaemagglutinin (PHA) Further dinitro chlorobenzene (DNCB) skin reactivity was meas ured being a sensitive in vivo parameter of cellular immune capacity The results showed a tendency towards high immune responsiveness in this family compared to the relatives by marriage who served as a control group

It appeared that also multiple autoimmune thyroid disease was present in this family in the form of Graves disease An association between thyroid disease and paraproteinaemia has inciden tally been described (2 27 33) It is of interest that also in autoimmune thyroid disease dysregulation of immune responsiveness has been suggested to be a pathogenetic factor (8)

STUDY POPULATION AND METHODS

Family The family relationship is shown in Fig 1 The parents of the first generation were deceased There were

Abbreviations Ig = immunoglobulin HPH = haemocyanin of Helix pomatia PHA = phytohaemagglutinin DNCB = dinitrochlorobenzene

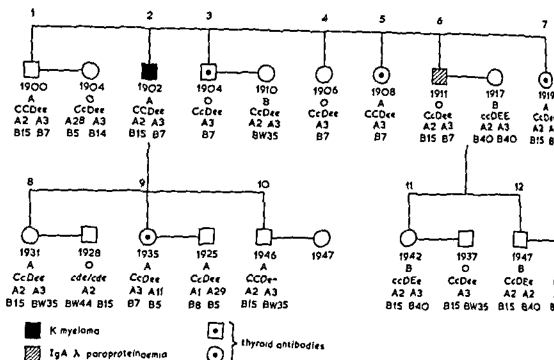


Fig 1 Relationships year of birth blood groups and HLA types of family members (numbered) and controls (relatives by marriage)

no known consanguinity and no indications of malignant paraproteinaemia or thyroid disease in these parents or the grandparents In one of four brothers in the first generation line a x myeloma was diagnosed half a year before this study after a period of backpain and a spontaneous fracture of the fibula (referred to us by P Blanksma and O de Vries Hospital Tjongerschans Heerenveen) He has since then been treated with six weekly courses of melphalan and prednisone He felt well at the time of study and had no complaints Sternal aspirate still showed preponderance of myeloma cells which had only x light chain determinants in the cytoplasma by immunofluorescence Immunoelectrophoresis of concentrated urine revealed x light chain proteinuria Serum Ig levels were low (Table I) Immunological studies were carried out during three weeks before a new cytostatic course

IgA λ paraproteinaemia and otherwise normal serum Ig levels were found in another brother (Table I) There was a slight increase in IgA λ containing plasma cells in the bone marrow No Bence Jones proteinuria was detected by immunoelectrophoresis of 40 times concentrated urine Bone X ray studies were normal He appeared healthy and had no complaints

The youngest sister (no 7) was a lively woman with a vascular bruit over a slight struma and a tremor of the hands but without eye symptoms She had no complaints appeared otherwise healthy and had a normal weight Thyroid hyperfunction was confirmed by a T_4 serum level of 17 4 μg/100 ml (normal 7 0–12 5) Serum thyroid antibodies were present as shown by strongly positive immunofluorescence of her serum against thyroid cytoplasma (presumably microsomal antibodies) (J A I Regional Public Health Laboratory Gronin munological studies were completed before tre

One sister (no 5) had undergone a partial tomy 20 years earlier because of thyroid hyp She and another brother (no 3) had weakly posi thyroid (cytoplasma) antibodies without signs hyper or hypofunction One brother and one sis abnormalities

Five children of the two brothers with parapro were also investigated One daughter of the pa x myeloma had weakly positive serum thyroid (ma) antibodies In all family members other s toantibodies were negative (rheumatoid antinuc tiparietal cell antimitochondrial and antismooth antibodies)

Available relatives by marriage of the family were without detectable disease and served as group (Fig 1)

HLA and blood group typing of family mem controls (Fig 1) was carried out by con techniques (J M van der Voort Beelen and J Sijpesteijn)

Serum Ig levels were determined by radioim fusion IgG subclass measurements (T Out Laboratory for the Blood Transfusion Service A dam) were performed by a slightly modified te according to van der Giessen et al (16) Results pressed as percentages of standard serum c ing 6 1 mg IgG_1 3 2 mg IgG_2 0 5 mg IgG_3 and IgG_4 per ml

Comparison of patients family members and controls

	x myeloma	IgA para proteinaemia	Family members	Controls
			Mean and range	
	74	65	50 2 (29–76)	48 9 (26–72)
(mg/100 ml)				
	473	1 397	1 479 (924–1 727)	1 369 (979–1 639)
	10	234	172 (70–312)	246 (10?–822)
	7	784	204 (70–357)	236 (113–414)
(% of standard serum)				
	25	130	149 (105–205)	139 (90–155)
	70	200	186 (50–320)	181 (105–250)
	25	130	147 (80–270)	139 (100–215)
	90	85	96 (30–200)	65 (35–130)
es (3 weeks)				
	6	8	9 1 (6–11)	7 1 (3–10)
	4	9	7 4 (4–11)	5 3 (3–7)
	2	9	7 4 (6–10)	5 7 (4–9)
	3	6	7 6 (6–10)	6 0 (1–9)
	5	7	7 1 (6–9)	4 9 (1–8)
	3	6	5 8 (4–7)	4 6 (0–10)
	2	5	5 9 (5–8)	3 7 (1–5)
nulation index			Median and range	
ts	1 2	2 9	1 2 (0 6–1 6)	1 1 (0 6–2 4)
ts	3 8	2 8	16 7 (2 5–28 9)	5 0 (1 4–7 9)
ts	–	3 0	22 8 (8 8–147 8)	6 7 (4 3–12 3)
nulation (dpm × 1000)	37	24	30 7 (20 4–80 2)	37 9 (24 7–80 3)
core (maximal range 0–12)	12	12	12 (3–12)	11 (1–12)
ubjects			8–10	7–8

ral immune response Immunization was done primary immunogen HPH (14 34) 1 mg sub- isly at weeks 0 and 6 Sera were collected at 2 3 6 8 and 14 IgM IgG IgA class specific subclass specific anti HPH titres were d by an enzyme linked immunosorbent assay e as previously described (34 35) Titres are ex as titre steps of doubling serum dilutions starting 0 = 0 for IgM and IgA and with 1 20 = 0 for IgG subclasses of IgG

ar immune response *DNCB skin reactivity* was d semiquantitatively by patch testing after sen n as previously described (4) The minimal score maximal 12 *HPH induced lymphocyte transfor* (6-day cultures ^{3}H thymidine incorporation) be l after immunization was done as previously de (14 36) Findings are expressed as a stimulation hich is the ratio between the cultures with and antigen *PHA induced lymphocyte transforma* day cultures ^{3}H thymidine incorporation) ex as dpm values were done as previously described

tical analysis was done using Student s *t* test led) for Ig and titre comparisons and Wilcoxon s m test (two-tailed) for comparison of indices of immunity Significant statistical difference was d at $p<0\ 05$

RESULTS

Humoral immune capacity

Serum Ig levels of family members did not differ from those of the controls (Table I) ($p>0\ 20$ for all classes and IgG subclasses) *Ig class specific and IgG subclass specific anti HPH titres* after primary and secondary immunization in family members without paraproteinaemia ($n=8$) were compared with those in the controls ($n=7$) (Figs 2 and 3) Mean values for all classes and subclasses were higher in the family at all points of time The difference was statistically significant at most points of time for IgG IgG_2 and IgG_4 anti HPH titres (p values depicted in Figs 2 and 3) Anti HPH titres three weeks after primary immunization in the two brothers with paraproteinaemia are compared with titres in the family and the control group in Table I Values in the patient with IgA para proteinaemia were within the range of his family Values in the patient with x myeloma were lower and within the range of the controls The values of 4

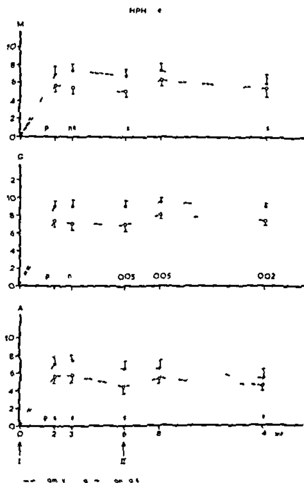


Fig 2 IgM IgG and IgA spec f c anti HPH t tre k net cs (mean±S E M) after primary (*I*) and secondary im mun zation (*II*) in 8 family members (●) and 7 controls (O) Titres are expressed as titre steps represent ng dou bl ng serum d lut ons *P* values above the various points of t me indicate stat stical s gn f cance (ns=not sign f cant)

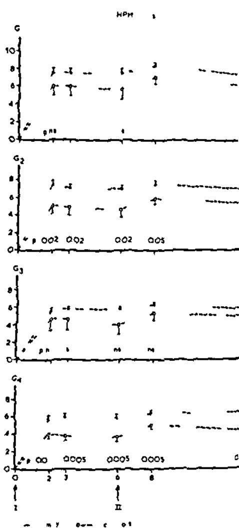


Fig 3 IgG $_{1,3,4}$ specific ant HPH t tre k ne ics family and controls Same presentat on as n Fig

family members with thyroid antibodies did not dif fer from those of the other 4

Cell ilar immune capacity

In vitro HPH induced lymphocyte transformation after immunization was significantly h gher in the family group than in the control group after primary as well as secondary immunization (Table I) *P* val ues were <0 05 at three weeks and <0 01 at eight weeks There was a wide variation of HPH induced lymphocyte transformation indices in the family group varying from the narrow range present in the control group to high values Although in the fami ly as a group this higher in vitro cellular reactivity to HPH was associated with higher anti HPH titres in vivo there was no direct correlat n be individual titres of any Ig class or subcl values of in vitro lymphocyte stimulation F members with signs of autoimmune thyroid d did not differ from the others Both brothers paraproteinaemia had values with n the range controls (Table I)

DNCB skin reactivity score (Table I) The dian score was higher in the fam ly than control group but the d fference was not s g (0 05<*p*<0 10) Both patients with parap aemia as well as the four fam ly members thyroid antibodies had score 12 the highest p ble

PHA induced lymphocyte transformation I) There was no difference between the f

...up and the control group Both patients with ...aproteinaemia had normal values

COMMENTS

...ameters of immune capacity were studied in a ...ily comprising 12 first and second-degree rela... Two family members had paraproteinaemia ... malignant) two had active autoimmune ...oid disease (Graves disease)—one at the time ... study and one in the past—and a further ... had weakly positive thyroid antibodies without ...ase

...e humoral immune response to a primary test ...en (HPH) was higher in this family than in the ...ols who were relatives by marriage of the ...y members This result could not have been ...icted on the basis of the (normal) serum Ig ...s in the family Considering in vitro antigen in... lymphocyte transformation as a sensitive ... of cellular immune capacity (15) this ...y showed also cellular hyperimmune respon...ess to haemocyanin Of the other measured ...neters of cellular immune capacity DNCB ...eactivity also tended to be high whereas PHA ...ed lymphocyte proliferation was normal ... induced lymphocyte proliferation capacity is ...ably less suitable to measure hyperimmune ...onsiveness because it is already a very strong ...lant at optimal dosage in normals

...e findings in this family show a certain re...lance to the situation in Balb/c mice which ...it humoral hyperimmune responsiveness to ...r with easily inducible plasma cell tumours ... Dysregulation of Ig synthesis has been ...sted in families with myeloma and macro...ulinaemia on *the basis of higher serum Ig levels* ... in control populations (13 22) In the family ...d here serum Ig levels were not clearly ele... However humoral immune responsiveness ...rds antigens is not necessarily related with ...n Ig levels The genetic control of humoral ...ine responsiveness in man is probably on two ...s general via the rate of Ig synthesis and more ...fic dependent on antigen structure (24) Rela... between serum Ig levels and specific immune ...onses have to our knowledge not been investi... in human families but Ig class specific im... responses to haemocyanin did not correlate ... serum Ig levels in non related normals (35) ...yperimmune responsiveness or a hyperactive Ig producing system or immune stimulation is probably not enough to make the subject more prone to develop a plasma cell tumour Transition from polyclonal to monoclonal hypergamma globulinaemia has been observed in patients with rheumatoid arthritis cirrhosis of the liver (9 40) and in animal models of autoimmunity (28 29) However in man the incidence of plasma cell tumours in these diseases is not clearly increased (10 19) A relation was found between myeloma and pernicious anaemia (23) but pernicious anaemia is associated with hypo and not with hypergamma globulinaemia (17) The second factor which seems necessary for the development of a plasma cell tumour is a susceptibility to oncogenesis of plasma cells (30 31)

Autoimmune thyroid disease includes Graves disease (8) Thyroid stimulating antibodies play a role together with diagnostically important thyroid specific microsomal and thyroglobulin antibodies An immune suppressor cell defect leading to uncon trolled immune responses towards thyroid tissue has been suggested (1 8)

It is tempting to suggest the presence of a general immune suppressor cell defect (32) in the family presented here on the basis of increased responses towards humoral and cellular test immunogens in vivo and in vitro Such a defect by leading to un controlled immune reactions to antigens including self antigens might explain the multiple occurrence of paraproteinaemia and thyroid disease in one generation of this family

HLA B7 and 15 were present in this family This is different from observed associations in Graves disease (B8) (18 21) myeloma (B5 B18) (3 12) and partly different from observations in benign para*proteinaemia (increased frequency of B7 and de*creased frequency of B15) (6) Immune responsive ness in man is probably related to the major his tocompatibility complex as in mice but a clear rela tionship between HLA types and immune respon siveness was not apparent (24)

It is concluded that humoral hyperimmune re sponsiveness in certain instances may be an im portant prerequisite for the development of human plasma cell tumours as is the case in the animal plasma cell tumour model Both patients with para proteinaemia in this family showed less signs of hyperimmune responsiveness and this might be explained by the fact that malignant and sometimes benign plasma cell tumours themselves depress

humoral and cellular immunity (5 7 11 20 35 36 37)

ADDENDUM

A third case of paraproteinaem a was diagnosed 3 years later in a sister of the two brothers with para proteinaemia (no 5) She had a history of thyroid hyperfunction and had been well until recently when she was adm tted to a hospital because of an acute major hemiplegia Cerebrovascular throm bosis was diagnosed Rout ne laboratory tests re vealed no abnormalities X ray of the chest was normal She was transferred to a nursing home and died of pneumonia and cardiac decompensation within 2 weeks A blood test shortly before death revealed no cryoglobulinaemia or paracoagulation Serum electrophoresis disclosed two faint bands in the beta gamma region Subsequent immuno electrophoresis showed a moderate amount of Bence Jones λ protein Urine could not be stud ed with immunoelectrophoresis but an Albustix test had been negative This does not exclude the pres ence of a significant Bence Jones proteinuria Serum Ig levels were IgG 720 IgA 60 and IgM 30 mg/100 ml ESR was 13 mm/l hour blood Hb 15 6 g/100 ml blood urea 5 5 mmol/l serum creatinine 85 μmol/l and total serum prote n 6 3 g/100 ml Serum thyroxine level was normal

Re examination of serum and urine stored 3 years earlier disclosed no abnormal bands on electrophoresis but immunoelectrophoresis with a panel of different Bence Jones antisera showed that a slight but distinct Bence Jones λ paraproteinaemia and proteinuria had been missed at that time by the antisera in use Serum Ig levels at that time were IgG 924 IgA 70 and IgM 70 mg/100 ml

This patient manifested in 3 years a slowly in creasing Bence Jones paraproteinaemia without overt signs of myelomatosis at the time of death She links in her person the thyroid disease and para proteinaemia which were both multiple but sepa rately present in her relatives Parameters of im mune capacity in this patient 3 years before death of probably arteriosclerotic cerebrovascular disease were excellent as compared to the controls and intermediate in the higher range observed in her family (CHPH titres 3 weeks after immunization G 7 M 7 A 6 G_1 7 G_2 7 G_3 5 G_4 5 HPH stimulation index 0 weeks 1 2 3 weeks 5 5 8 weeks 18 8 PHA 28 800 DNCB 9) (Table I)

ACKNOWLEDGEMENT

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REFERENCES

1 Aoki H P nnamanen K M & De Groo Stud es on suppressor cell funct on n thyro d J Cl n Endocrinol Metab 48 803 1979
2 ten Berge B S Paraprote naem e p 18 State Univers ty of Gron ngen 1965
3 Bertrams J Kuwert E Bohme U Re Gallmeyer W H Wetter O & Sm dt C ant gens in Hodgk n s d sease and mul ple Increased frequency of W18 in both d ease Ant gens ? 41 197?
4 Bleumink E Nater J P Schrafford Koo The T H A standard method for DNCB t on test ng in pat ents w th neoplasma 33 911 1974
5 Broder S Humphrey R Durm M Black Meade B Golman G Strober W & Wa T Impa red synthes s of polyclonal (non te n) immunoglobul ns by circulat ng lym from pat ents w th mult ple myeloma R pressor cells N Engl J Med ?93 887 1975
6 van Camp B G K Cole J & Peeterman HLA ant gens and homogeneous immuno Cl n Immunol Immunopathol 7 315 1977
7 Cone L & Uhr J W Immunolog cal d disorders associated w th chron c l leukem a and mult ple myeloma J Cl 43 2?41 1964
8 Don ach D & Roitt I M Thyro d a d sease In Cl n cal aspects of immunology H Gell R R A Coombs and P J Lachma ter 47 Blackwell Oxford 1975
9 Dryll A Rousselet F Ryckewaert A M F Duquet M & De Sèze S Rhuma matoire et paraproté nes en dehors du myél la malad e de Waldenstrom Etude de 18 obse personelles de cette associat on Sem H 45 2135 1969
10 Englisova M Engl s M & Hoen g V Inci paraprote ns in chronic l ver d sea es Sca troenterol 3 413 1968
11 Fahey J L Scogg ns R Utz J P & Szw Infect on ant body response and gamma components in mult ple myeloma and globul naem a Am J Med 35 698 1963
12 Festen J J M Marrink J Kaars S van Loghem E N jenhu s L E & Mandema study on the assoc at on between myeloma immunoglobul n allotypes HLA and bl Immunogenet cs 3 ?01 1976
13 Festen J J M Marrink J de Waard Ko & Mandema E Immunoglobul ns in fa myeloma pat ents Scand J Immunol 6 88
14 de Gast G C The T H & Sn jder J A human immune response to a haemocya pomat a Acta Med Scand 194 303 1973

eha R S Schneeberger E Rosen F S & ..lerler E In eract on of human thymus-derived and ion-thymus-derived lymphocytes n v tro Induct on of prol fera on and ant body synthesis in lympho-y es by a soluble factor released from ant gen t mula ed T lymphocytes J Exp Med 138 1?30 973

an der G essen M Reering Brongers E E & Al ra van Veen T Quant tat on of Ig classes and IgG ubclasses n sera of pat ents w th a variety of immu oglobul n def c enc es and the r relat ves Cl n Im iunol Immunopathol 5 388 1976

nsburg A & Mull nox F Pern c ous anaemia and ionoclonal gammopathy n a pat ent with IgA def ency Am J Med 48 787 1970

rumet F C Payne R O Kon shi J & Kriss J HL A ant gens as markers for d sease suscept b li and auto mmun ty n Graves d sease J Cl n En ocrinol Metab 39 1115 1974

allen J D screte gammaglobul n (M) components serum Cl n cal study of 150 subjects w thout yelomatos s Acta Med Scand (Suppl) 467 1966

iams J E Alexen an R Hersh E M & M g re Ph Immune funct on in mult ple myeloma Im ired respons veness to keyhole l mpet hemocyan n m Med Assoc J 104 ?89 1971

nne W J Gray R S Morris P J & T ng A rrelat on of HLA and thyro d ant bod es w th cl n course of thyrotox cos s treated w th anti thyro d ugs Lancet ? 898 1977

iff M W & Hymans W Immunoglobul n alys s in fam l es of macroglobul naem a pat ents in Exp Immunol 5 479 1969

rsson S O Myeloma and pern c ous anaem a ta Med Scand 172 195 196?

ackay I R Wh tt ngham S & Ta t B Genetic n rol of immune responsiveness n man Vox Sang a el) 3? 10 1977

aldonado J E & Kyle R A Fam l al myeloma port of 8 fam l es and a study of serum prote ns in eir relatives Am J Med 57 875 1974

leberg H Johansson B G & Berl n S O Im unoglobul n analys s in fam l es of myeloma pa nts Acta Med Scand 196 361 1974

serman E F Natural history of mult ple myeloma fo e rad olog cal ev dence of d sease Rad ology 157 1958

?8 — Mult ple myeloma and related plasma cell dys-cras as In Immunolog cal d seases (ed M Samter) chapter ?6 Little Brown & Co Boston 1971

?9 Porter D D D xon F J & Larson A E The development of a myeloma l ke cond t on in m nk w th aleut an disease Blood 25 736 1965

30 Potter M Immunoglobul n produc ng tumors and myeloma prote ns of m ce Phys ol Rev 5? 631 197?

31 Salmon S E & Sel gmann M B-cell neoplas a in man Lancet ? 1?30 1974

3? S egal F P Suppressors in the network of mmun ty N Engl J Med ?98 10? 1978

33 Waldenstrom J G Monoclonal and polyclonal hypergammaglobul naem a Cl n cal and b ological s gn f cance p 18? Cambridge Un vers ty Press London 1968

34 We ts J de Gast G C The T H Essel nk M T Deelder A M Petrov c M & Mandema E Class-spec f c ant body t tres (ELISA) aga nst the primary immunogen Hel x pomat a haemocyan n (HPH) n man Cl n Exp Immunol 3? 443 1978

35 Weits J de Gast G C The T H Essel nk M T van der G essen M & Mandema E Class and sub-class spec f c ant body response to hemocyan n n non mal gnant paraprote nem a J Lab Cl n Med 94 458 1979

36 We ts J de Gast G C The T H Essel nk M T & Mandema E Cellular mmunocompetence in asymptomat c paraproteinaem a Acta Med Scand ?0? 17 1977

37 We ts J de Gast G C The T H Marrink J & Mandema E Immune response in asymptomat c paraprote nem a I Primary and secondary ant body response to Hel x pomat a hemocyan n Scand J Im munol 5 1163 1976

38 Will ams R C Erickson J L Polesky H F & Swa m W R Stud es of monoclonal immunoglobu l ns (M-components) n var ous k ndreds Ann Intern Med 67 309 1967

39 Yamada H Mashburn L T Takakura K & Hol lander V P The correlat on between plasma cell tumor development and ant body response in nbred strains of m ce Proc Soc Exp B ol Med 131 947 1969

40 Zawadzk Z A & Edwards G A Dysimmuno-globul nem a assoc ated w th hepatob liary d sorders Am J Med 48 196 1970

Acta Med Scand 208 177–182 1980

Demonstration and Partial Characterization of an Atypical Protein in the Urine of a Patient with Primary Amyloidosis

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RACT A paraprotein has been isolated from ine of a patient with primary amyloidosis Im ogically it was classified as a free λ light chain iolecular weight was 22 500 daltons N terminal acid analysis demonstrated homology with variable subgroup in 19 of the first 20 amino Extensive homology with λ IV chains was istrated also in the hypervariable region of ht chain An antiserum produced against the rotein was rendered idiotype specific by ab n with pooled human light chains This an n stained tissue specimen from the rectum and of the patient by the indirect immunofluores technique This strongly indicates that the free t chains that can be isolated from the urine are eposited in the tissues as amyloid substance

ords amino acid sequence immunohistochemistry y amyloidosis urinary amyloid protein
Med Scand 208 177 1980

fication of amyloidosis is rather complex and sing From the clinical point of view amy is has been divided into three major classes imary amyloidosis without detectable un ng disorder 2) Secondary amyloidosis that is iated with systemic diseases or chronic infec 3) A form of amyloidosis associated with omatosis (3)

om the histochemical point of view amy sis can also be classified according to the of amyloid deposits in the walls of the blood ls The perireticular amyloidosis is usually l in the intimal layer of the blood vessels eas the pericollagen amyloidosis is located to dventitial layers of the vascular bed Amyloid ance deposits in tissues can be demonstrated after Congo red staining giving a green birefrin gence (18)

The amyloid substance has been defined as ex tracellular material which is composed mainly of proteins with a fibrillar structure X ray crystallo-graphy has shown that the fibrillar material is ar ranged in a β pleated structure The solubilization of these fibril proteins has rendered them accessible to investigation by biochemical techniques Until now three major classes of amyloid fibril proteins have been characterized

1 *A group of proteins with varying molecular* weight from about 5 000 to 9 000 daltons (12 18) The origin of these proteins is unknown they are unrelated to immunoglobulins and are termed pro tein AA (26) Protein AA shows antigenic cross reaction with a serum α_1 globulin which has been regarded as a precursor protein of the amyloid fibril protein AA (26) Studies have further shown that protein AA is the major component in the amyloid fibrils from patients with secondary amyloidosis

2 The second class of amyloid fibril proteins consists of immunoglobulin light chains or light chain fragments (AIO) (18) AIO proteins have mostly been seen in amyloid fibrils of patients with primary or myeloma associated amyloidosis So far only two amyloid related urinary proteins one κ and one λ chain have been extensively studied (26)

3 Evidence has been presented supporting the

Abbreviations PAGE – polyacrylamide gel electro-phoresis SDS sodium dodecyl sulfate DI differ ence index ELISA – enzyme linked immunosorbent as say OD optical density PBS – phosphate buffered saline

hypothesis that the amyloid P component (protein AP) also is an integral part of the amyloid fibril (7).

We have isolated a free λ light chain from the urine of a patient with a well established primary amyloidosis. It is the aim of this report to characterize further this protein both immunologically and with respect to its amino acid sequences.

CASE REPORT

A man, born in 1916, was admitted to the Department of Medicine, Østfold County Hospital, because of dyspnea during exercise and pretibial edema. He also complained of bowel symptoms, including obstipation and periodic diarrhea, anorexia and loss of initiative.

Physical examination revealed markedly hypertrophic parotides, enlarged submandibular glands and macroglossia. The skin and nails were dry and atrophied. The heart was large, with a relative cardiac volume exceeding the *upper limit of the range of reference.* No cardiac murmurs were heard.

The blood pressure was normal (RR 150/90). Hb 11.5 g/100 ml, ESR 72 mm/h, RBC 4.7×10¹²/l, WBC 5.6×10⁹/l and platelets 190×10⁹/l. Repeated peripheral blood smears were all normal. Bone marrow aspirate specimens contained on several occasions less than 5% plasma *cells. Serum iron and total iron binding capacity, serum* vitamin B₁₂ and folic acid as well as thyroid function tests including T-3, T-4, TSH and TRH were within the range of reference. Liver function tests and liver enzymes including ASAT, ALAT, γ-GT and ALP were all normal. No protein anomalies were demonstrated by routine electrophoresis on cellulose acetate. Nor was any M component *demonstrated by agarose gel electrophoresis of* serum.

The patient's renal function was normal as evaluated by creatinine and creatinine clearance. Electrolytes, serum triglycerides, cholesterol and lipoproteins were also normal. Electrophoresis of concentrated urine, however, disclosed a mixed proteinuria including albumin and a paraprotein *of λ light chain nature (0.7 g/l). Endocrine pancre*as insufficiency could not be demonstrated as fasting blood glucose and a glucose tolerance test were within the range of reference. His exocrine pancreatic function was not tested. Antinuclear factor, Waaler and Ra Latex tests were negative.

X-ray studies of colon demonstrated small diverticles in *the sigmoid part. X-ray studies of the skeleton did not* reveal osteolytic changes or osteoporosis. However, small *changes due to osteoarthritis were detected in the left hip.* Scintiscans of the skeleton were normal, as well as scintiphotos of liver and spleen.

Biopsy of the temporal artery was normal. Biopsies of rectum, skin and liver, however, demonstrated amyloid infiltration located *to the vascular walls, but also with* small infiltration of the adventitial regions. Since no sys*temic disease, chronic infection or myelomatosis were* detected, the diagnosis of "primary amyloidosis" was made. No treatment except regular cardiac insufficiency regimen had been instituted.

MATERIALS AND METHOD

Serum was taken from the patient by regular *puncture. Urine was collected on several occa*sions ally 24-hour collections.

Electrophoretic and immunological studies

Electrophoresis of serum, urine and the vario obtained after column separation was perfor in 1% agarose gel as described by Johansson tion, some studies were performed by polyacr electrophoresis (PAGE) mainly to test the pu fractions. Sodium dodecyl sulfate (SDS)-PA were performed to estimate the molecular we amyloid protein (28). The immunological te ried out with conventional double diffusion cording to Ouchterlony (17). (A part of the a obtained from Dacopatts and Behringwerke.)

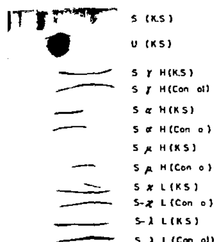
Isolation of the free λ light chain from the urine

The paraprotein was isolated from the urine in ent ways. In order to remove albumin contam used column affinity chromatography with a 4B Blue Dextran conjugate as originally de Travis and Pannel (25), but with some minor mo (29). Urine first dialysed against saline (0.9% *was applied to the column. One ml of concen*was applied to the column for each run. The eluted in two steps, namely with 0.1 M Tris-H and 6 M urea. The eluates were then conce red alysis against saline in vacuum. In this wa HCl eluate contained the amyloid protein. Th eluate contained the albumin as evidenced by *electrophoresis in agarose gel demonstrating* band. Immunoelectrophoresis of the concen HCl eluate against anti λ and anti κ sera (fr demonstrated that the amyloid protein was n nature. A faint κ reaction was obtained occasio

In some experiments the urine was dial d stilled water and lyophilized. The lyophiliz *was dissolved in 0.05 M Tris HCl (pH 7.6)* an ated on a Sephadex G 200 column. A low we ght fraction (approximately ... daltons) light chains was recovered. The protein recove fraction was approximately 0.25 g/l urine. onstrated one single band in agarose gel. Imm ly the fraction contained mainly peptide chains *ture, but traces of κ chains were also demon*stra κ chains were removed by applying the isolated fraction on an immunosorbent column con mobilized rabbit anti human κ light chain an bod purified fraction gave no reaction against κ lig immunoelectrophoresis. This protein fraction d onstrated one band in PAGE.

Studies on total amino acids

The purified amyloid protein was subjected t studies including analysis of total amino acid wh determined on a BioCal BC 200 amino acid a nected to an Autolab Computing Integrator S tem AA) after acid hydrolysis of the samples a for 24 hours (22, 23).



Agarose gel electrophores s of serum (*S*) and urine f the pat ent (*K S*) show ng normal serum pattern as e urinary excret on of a paraprote n class f ed munoelec rophores s as lambda l ght cha ns

amino ac d relatedness of the isolated free λ l ght w h other λ and κ l ght cha ns was stud ed after tion of the difference ndex (DI) of Metzger et al

inal am no ac d seq ence anal s s

n nal analys s was performed w th a JAS-47K JEOL nce Analyzer us ng 0 1 M Quad ol buffer with ene 1 0 nmols were appl ed to the analyzer The lth ohydan o n am no ac ds were analysed on th n hroma ography and gas chromatography (23)

rum

tiserum was raised aga nst the purif ed free λ l ght n a rabb t The ant serum was rendered d otype c after absorp on on two mmunosorbent columns arose 4B) to wh ch were coupled l ght cha ns so- from pooled human IgG and human serum respec

e l nked mmunoso bent assa (ELISA) for tes ng d otyp c spe f c of the an serum

est was performed in d sposable polystyrene tubes IC N1007 Denmark) All incubat ons were per d at room temperature The tubes were coated by a on for two hours w h 1 0 ml of a solut on of n pooled l ght cha ns and solated Bence Jones λ hains in a coat ng buffer cons st ng of 0 05 M sod um na e buffer pH 9 6 w th 0 05% NaN₃ After wash ree times w h 0 9% NaCl w th 0 05% Tween 20 the were incubated for 6–8 hours w th 0 1 ml of an m in phospha e buffered sal ne (PBS) w h 0 05% n 20 and 0 05% NaN After th s ncubat on the we e wa hed as described above and ncubated w th l of swine ant rabb t IgG ant bod es conjugated w th ne phosphatase (Orion Finland) The conjugate was used n a dilut on of 1/500 w h PBS contain ng 0 05 Tween 0 and 0 05% NaN₃ The ncubation t me wa 10–15 hours

After subsequent wash ng as described abo e 1 0 ml of the substrate solut on p n trophenylphospha e (1 mg/ml in 1 M d ethanolam ne HCl buffer pH 9 8 was added to the tubes and the enzyma c reac on was s opped by add ng 100 μl of 5 M NaOH to the tubes The react on was stopped before the solut on had an op cal dens ty (OD) 1 at 400 nm and the OD_{400} measured was referred to a standard t me 100 m n a sum ng a l near react on rate

Id p c st d es of an l d depo s

Sect ons from rectum and l er b ops es were cut n a m crotome After wash ng in PBS the sect ons were per m tted to react w th the ant d o ype ant bod es at room temperature fo 0 m n After a new wash n n PBS the sect ons were reacted w h a FITC-conjugated goat an rabb t mmunoglobul n ant serum (Behringwerke Mar burg Lahn W Germany) for 0 m n at room temperature After wash ng in PBS the sect ons were stud ed n a Le tz Orthoplan M croscope w th an Osram HBO- 00 h gh pressure mercury vapo burner l ght sou ce and a Le tz Vert cal Illum nator The stud es were repeated after the ant d otype ant serum had been peps n-d gested as de scribed earl er (4) Sect ons from rectum and l er b ops es from pat ents w th o her d sorde s than am lo dos s were sta ned w th the same an sera

RESULTS

Electropl oret c a d n n log c st d es

Agarose gel electrophores s of serum from the pa t ent was normal w thout any paraprote n (Fig 1) Concentrated urine ho ever disclosed parapro te n excret on n addit on to small concentrat ons

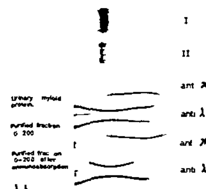


Fig 2 Electrophores s of freeze-dried amylo d pro e n from urine (*I*) after G 00 gel filtra on (*II*) Immunoelec trophores s demonstrates that the purif ed G 200 fract on after mmunoabsorpt on w th ant kappa serum contains lambda l ght chains only The bottom well conta ns a lambda l ght cha n control

Table I *Total amino acid composition of the patient's amyloid protein compared to the composition of lambda and kappa light chains*

	Amyloid protein	Lambda L	Kappa L
Asp	20	14	20
Thr	21	21	19
Ser	26	31	27
Glu	29	21	26
Pro	16	15	11
Gly	15	15	13
Ala	15	18	12
1/2 Cys	5	5	5
Val	14	17	13
Met	2	1	1
Ile	5	5	9
Leu	14	13	15
Tyr	7	8	10
Phe	5	5	9
His	3	3	3
Lys	11	12	13
Arg	6	6	6
Glucosamine	3	–	–
Galactosamine	1	–	–

* The calculation is based on a total of 213 residues and a mol wt of about 23000 daltons (Res/100 213)

Table II *Test for anti idiotypic specificity [illegible] sorbed antiserum against the urinary λ L [illegible] and other isolated human Ig light chains by ELISA method*

The antiserum was used in a dilution of 1/100

Coat (1 μg/ml)	OD/100 min
Pooled light chains*	0 07
Urinary λ chain	1 63
HBJ, VλII*	0 08
HBJ, VλI*	0 06
HBJ VλIII*	0 03
Buffer	0 07

* Isolated from reduced and alkylated pooled [illegible]
* Isolated human Bence Jones proteins with [illegible] subgroup

Control experiments in which tubes with the sa[illegible] above were incubated with conjugate gave an [illegible] min less than 0 1

of albumin and an unknown trace contamination of protein nature (Fig 1) By immunoelectrophoresis the paraprotein had mainly λ specificities but occasionally a positive κ reaction was seen (Fig 1)

Fig 2 shows the paraprotein preparation after purification on a G 200 column with subsequent column affinity chromatography demonstrating one single band by electrophoresis in agarose gel and PAGE

SDS-PAGE studies with marker proteins indicated a molecular weight close to 22 500 daltons

Total amino acid analysis

Total amino acid analysis of the purified paraprotein preparation demonstrated a composition similar to λ light chain (Table I)

Calculation of the DI did not contribute significantly to the identification since DI values of amyloid paraprotein/λ L amyloid paraprotein/κ L and λ L/κ L all were very close to 10 (9 5 10 5 and 10.5 respectively) Interestingly both galactosamine and glucosamine were detected in the amyloid protein (Table I)

Partial amino acid sequence analysis

Partial N terminal amino acid sequence analysis of the first 31 amino acids of the amyloid protein was

NH–Tyr-Glu Leu Thr Gln Pro-Pro-Ser V[illegible]

Val Ser Pro-Gly Gln-Thr Ala Ser Ile/Leu Th[illegible]

(Ser)-Gly Asp-( )-Leu Gly Asp-Glu Tyr [illegible]

In position 25 no amino acid residue coul[d be iden]tified with certainty Only one amino ac[id] was detected in each position except in pos[ition] where both isoleucine and leucine were d[etected] The amino acid sequence revealed that th[e] is homologous to a λ IV immunoglobulin l[ight chain] (16) Among the 30 amino acid residues 26 [are iden]tical The N terminal sequence is also ve[ry similar] to an AIO protein isolated from the sp[leen of a] patient with primary amyloidosis (27)

Immunofluorescence staining of sections from rectum and liver biopsies

The antiserum was idiotype specific as [illegible] with the immunogen (the free urinary λ li[ght chain]) but not against pooled human light chains [or] different free λ light chains with different [illegible] subgroups (Table II)

The sections from the rectum and liver [of the] patient stained specifically with the a[nti idiotype] antiserum indicating that the parapro[tein dem]onstrated in the urine might be the same [as the] deposited amyloid substance in the tissues [illegible] and liver biopsies from patients with other [illegible] than amyloidosis did not stain positively w[ith the] anti idiotype antiserum

DISCUSSION

[...]ave isolated an amyloid protein with a molecu[...] weight of 22 500 daltons from the urine of a [...]nt with primary amyloidosis The protein has [...] purified and N terminal analyses revealed [...]t belongs to the λ IV subgroup

[...]en comparing this protein with the AIO fibril [...]m 808 (26) the N terminal amino acid se[...]ce up to position 20 is identical except for an [...]ange of aspartic to glutamic acid residue in [...]ion 2 The two other amyloid related Bence [...]s proteins reported in (26) have a quite different [...]rminal amino acid sequence but both λ chains [...] however a tyrosine residue in position 30 [...]h has been suggested to be of special signifi[...]

[...]other rather unusual feature of this Bence [...] protein is the content of glucosamine and [...]tosamine Of the homogeneous light chains [...] κ or λ type Bence Jones proteins or myeloma [...]chains analysed only about 15% have been [...] to contain carbohydrate (6)

[...]e relative contribution to the pathogenesis of [...]idosis by proteins of immunoglobulin nature [...] and non immunoglobulin origin (viz AA) is [...] active investigation In vitro studies have [...]n that several of these proteins will form fibrils [...] the properties of amyloid fibrils such as affini[...] Congo red and green birefringence after such [...]ng (12)

[...]nner et al (5) gave the first proof by sequence [...]sis that some human amyloid fibrils are [...]logous in structure with κ light chains (κ I [...]roup) Terry et al (24) also have demonstrated [...]ity between urinary Bence Jones light chains [...]ains) and the predominant protein present in [...] amyloid deposits This Bence Jones protein [...]gnated Tew) was subsequently sequenced by [...]am et al (19)

[...]e anti idiotype antiserum used in this study [...]ed no reactivity against pooled light chains and [...] isolated human Bence Jones proteins of Vλ [...]ble subgroup I II and III These results strong[...] indicate anti idiotypic specificity of the anti[...]m By means of this specific antiserum and [...]ect immunofluorescence technique we were [...] to prove that the same light chains as were [...]ted from the urine of our paient is also depos[...] in tissues as amyloid substance It is of in[...]t that some light chains with certain variable [...]roups tend to be associated with amyloidosis closer than other light chains Our study indicates that λ IV light chains are also amyloidogenic

Amyloid deposition of light chains or light chain fragments have only been observed in man (12) Casein injections have long been used for experimental induction of amyloidosis in mice (12) It has been postulated that the endotoxin of E coli which often contaminates casein may be the factor that causes induction (1)

Since one type of amyloidosis in man is related to immunoglobulin light chain deposition one might speculate whether amyloidosis is related to the B cell system alone or to disturbances in the T cell suppressor and helper cell systems which are involved in the regulation of B cell responses to certain antigens Some investigators have reported on an increase in B cell proliferation of spleen cells in mice during and after amyloid deposition probably due to polyclonal B cell activation (21) The T lymphocyte responses to phytohemagglutinin both in man and mice have however shown no distinct abnormalities in two studies (2 20) indicating normal T lymphocyte functions

λ Light chains as observed in this study are probably more commonly associated with amyloidosis than κ chains (12)

Clinically the symptoms commonly associated with amyloidosis are fatigue weight loss ankle edema dyspnea parasthesias hoarseness and occasionally gross bleeding All these symptoms except bleeding were present in our patient On physical examination especially the macroglossia and enlargement of the submandibular glands were extremely impressive

The treatment of amyloidosis patients is far from satisfactory Since at least part of the amyloid substance contains light chains or light chain fragments which are produced by plasma cells it has seemed reasonable to treat amyloidosis with alkylating agents that are effective against diseases characterized by proliferation of neoplastic plasma cells

Two patients with primary amyloidosis have indeed benefited from such therapy (10 14) with melphalan prednisone and D-penicillamine However a rapidly developing fatal leukemia has appeared during melphalan therapy in patients with amyloidosis (11) Our patient did not show any significant increase in plasma cells and we therefore decided not to institute any chemotherapy This decision is in accordance with the recent double

bl nd study by Kyle and Greipp (13) who found no s gn f cant difference n survival rate between p t ents g ven placebo and amylo d pat ents treated with melphalan and predn sone

REFERENCES

1 Barth W F Gordon J K & W llerson J T Amylo dos s nduced n m ce by E col endotox n Sc ence 16? 694 1968

? Bricett A B Cathcart E S & Cohen A S Lymphocyte transformat on and amylo dos s An mmunolog c study of 14 pat ents w th b opsy proved d sease Int Arch Allergy Appl Immunol 44 349 1973

3 Cohen A S Amylo dos s N Engl J Med ?77 5?? 574 6?8 1967

4 Førre Ø T Stud es of the ant gen comb n ng (var able) reg on of human immunog obul ns Thes s Un vers ty of Oslo Oslo 1977

5 Glenner G G Harada W T M Isersky C & Page D Amylo d f bril prote ns proof of homology w th immunoglobul n l ght cha ns by sequence analys s Sc ence 17? 1150 1971

6 Garver F A Chang L Mendd no J Isobe T & Ossermann E Primary structure of a deleted human lambda type mmunoglobul n l ght cha n conta n ng carbohydrate Prote n Sm lambda Proc Nat Acad Sci USA 7? 4559 1975

7 Holck M Husby G Sletten K & Natv g J B The amylo d P component (prote n AP)—an ntegral part of the amylo d substance? Scand J Immunol 10 55 1979

8 Husby G Natv g J B & Slet en K New th rd class of amylo d f br l prote n J Exp Med 139 773 1974

9 Johansson B G Agarose gel electropho es s Scand J Cl n Lab In est (Suppl) 1?4 7 197?

10 Jones N F H lton P J Tighe J R et al Treat ment of primary renal amylo dos s w th melphalan Lancet 616 197

11 Kyle R A P erre R V Bayrd E D et al Pri mary amylo dos s and acute leukem a assoc ated w th melphalan therapy Blood 44 333 1974

12 Kyle R A & Bayrd E D Amylo dos s In The monoclonal gammopath es Amer Lecture Series p 995 Thomas Spr ngf eld 1976

13 Kyle R A & Gre pp P R Primary system c amylo dos s Comparison of melphalan and pred n sone versus placebo Blood 5? 818 1978

14 Less n L S Hallal J Burkholder P et al structural s ud es of the role of the reticuloend cell n the cl n cal resolut on of amylo d sis Cl n Res ?0 51? 197?

15 Metzger H Shap ro M B Mos mann J E Assessment of compos t onal rela edne prote ns Nature ?19 1166 1968

16 M lste n C Clegg J B & Jar s J M A procedu e for the fract onat on of the tryp c of the C term nal half of mmunoglobu n I g B ochem J 110 631 1968

17 Ouchterlony O D ffus on n gel me hod munolog cal analys s Progr Allergy 5 1 195

18 Putnam F W In The plasma p o e ns vol 139 141 Academ c Press New Yo k 1977

19 Putnam F W Wh tle E J Jr Paule al C Am no ac d sequence of a κ Bence a ca e of primary amylo do s B ochem ry 1973

?0 Sche nberg M A & Catchart E S Casein exper mental amylo dos s III Response to allogen c cells and graft ver us host reaction mur ne model Immunology ?7 953 1974

21 Amylo d d sease and polyclonal B-cell (Abstr) Cl n Res 3 34? A 1975

22 Sletten K Ch stensen T B & Brandt Human secretory component III 12 783 1975

?3 Sletten K Husby G & Natv g J B The am no ac d sequence of an amylo d f bril pro of unusual s ze (64 res dues) B ochem B Commun 69 19 1976

?4 Terry W D Page D L K muea S e al tural dent ty of Bence Jones and amyloid fib te ns n a pat ent w th plasma cell dyscra amylo dos s J Cl n Invest 5? 1?76 12 6 19

25 Trav s J & Pannel R Sele t e remo al of from plasma by aff n ty chroma ography Cl Acta 49 49 1973

26 Wegel us O & Pasternack A In Amyl E F Ossermann) p ?21 Academ c Pres York and London 1976

?7 Westermark P Natv g J B Anders R F Coex stence of prote n AA and mmunoglob cha n fragments n amylo d f brils Scand J Im 5 31 1976

28 W lle L E Stud es on serum pre alpha Thes s Un vers ty of Oslo O lo 1977

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The Epidemiology of Thyrotoxicosis in Denmark

Incidence and Geographical Variation in the Funen Region 1972–1974

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RACT In a study based on a review of all d function tests performed in the Funen region mark over a three year period, from Jan 1, o Dec 31 1974 the annual incidence rates of oxicosis were found to be 46 5/100 000 for n and 8 7/100 000 for men In both sexes the ecific rates rose with age An analysis of the phical distribution of the cases showed a sig ntly lower incidence rate among women from an than from rural areas It is estimated that e time risk of developing thyrotoxicosis is 5% men and 1% for men and that the prevalence existing and previously diagnosed thyro is is 1 4% for Danish women and 0 3% for men

rds thyrotoxicosis incidence geographical varia

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toxicosis exhibits several characteristic epi logical features with different incidence rates two sexes and within different geographical In addition earlier studies have described rary rises in incidence (7) and have indicated e age distribution of new cases of thyrotoxi has undergone certain variations (8 10)

s study has been undertaken to give a current ation of the epidemiology of thyrotoxicosis in anish population Contrary to previous studies resent survey also includes cases diagnosed le hospitals

STUDY POPULATION

opulation studied was that of the Funen region sing approximately 450 000 inhabitants They form ographically representative sample of 9% of the Danish population (Green unpublished paper) The covered the period Jan 1 1972 – Dec 31 1974

The Funen region forms a geographically well defined administrative unit under one health authority The Regional Hospital—where all specialities are represented—is situated in central Odense with 10 smaller hospitals in the surrounding area

Endemic goitre does not occur in the Funen region *Demographic data have been obtained from Danmarks* Statistik (3 4 5)

MATERIAL AND METHODS

During the study period thyroid function tests were performed by the hospital laboratories in Svendborg and Odense toward the end of the study exclusively by the Department of Clinical Chemistry Odense Hospital During a brief part of the study one of the hospitals referred its thyroid function tests to a laboratory outside the Funen region

The function tests comprised serum protein bound iodine serum Thyroxine T_3-resin test and serum triiodine thyronine Basal metabolic rate was estimated occasionally but not as a routine test

When reviewing all the thyroid function tests performed throughout the three year period we identified the patients with raised values i e values above the normal reference range used by the laboratories Additionally patients from the hospital referring the tests to a laboratory outside Funen were separately investigated and included in the study if the criteria were fulfilled Finally basal metabolic rate tests performed were subjected to a special review in order to identify patients who had underwent this test only

For each patient showing raised values an enquiry was made to the referring physician or hospital department in order to check whether the diagnosis of thyrotoxicosis had been made and if so to obtain the time of the first diagnosis and the type of treatment instituted In a few cases this information had to be requested from the patients themselves In this way a register was established of all newly diagnosed cases of thyrotoxicosis with treatment instituted in the Funen region over the period Jan 1 1972 to Dec 31 1974 No attempt has been made to divide the cases into subgroups such as Graves disease toxic adenoma etc

Analyses

The incidence of thyrotoxicosis is expressed as the average annual rates specified for age and sex Standard errors

Table I *Newly diagnosed cases of thyrotoxicosis in the Funen region Denmark 1972–74*

Age group (y)	Males: No of cases 1972–74	Males: Population[a]	Males: Mean annual rate (per 10^5)	Males: 1 S E	Females: No of cases 1972–74	Females: Population[a]	Females: Mean annual rate (per 10^5)	Females: 1 S E
0–9	–	34 617	0		–	32 585	0	
10–19	2	34 042	2 0	1 35	5	32 150	5 2	2 35
20–29	5	34 239	4 9	2 15	33	32 130	34 2	5 95
30–39	8	26 263	10 2	3 60	42	25 890	54 1	8 35
40–49	13	24 848	17 4	4 85	52	25 275	69 6	9 50
50–59	7	25 431	9 2	3 45	62	26 175	79 0	10 00
60–69	8	22 396	11 9	4 20	49	23 833	68 5	9 75
70–79	9	12 812	23 4	7 80	47	15 836	98 9	14 45
80–	5	4 813	34 6	15 50	17	6 429	88 1	21 40
Total	57	219 461	8 7	1 15	307	220 303	46 5	2 65

[a] Mean for each of the years 1972 1973 and 1974

(S E) of these rates are calculated from the approximate formula

$$\frac{1}{3}\sqrt{\frac{pq}{n}}$$

in which p = the calculated three year rate $q = 1-p$ and n = the size of the age group (expressed as the average of the size in the three years of study)

In order to analyse the geographical distribution all cases of thyrotoxicosis have been distributed within three regions on the basis of their postal address at the time of diagnosis Region I (city area) the municipality of Odense region II (town area) the municipalities of Svendborg Middelfart Nyborg and Fåborg combined region III (rural area) the rest of the total Funen region

The population of each region has been standardized using the entire population of Funen as the standard Comparisons between two standardized three year rates were made by calculating the standardized normal deviation (1) using a significance level of 5% The cumulative morbidity risk has been calculated according to the principle of the life table method (2)

RESULTS

The study comprises 364 cases 307 wome
men In 323 (89%) of the cases the diag
established during admission to a hospital
and sex distribution was the same for th
diagnosed in or outside hospital In only
was the diagnosis of thyrotoxicosis establ
treatment instituted on the basis of th
metabolic rate test alone

As no differences were found between
tions made in 1972 1973 and 1974 the data
whole period have been pooled for analysis
shows the age and sex distribution of cases
corresponding incidence rates A significa
ence is seen between the sexes the overall
incidence in women being 46 5 (1 S E =
100 000 and in men 8 7 (1 S E = 1 15) per 1
Distinct age variations are also seen in bo

Table II *Geographical distribution of the cases*

	Area I (Odense)	Area II (Svendborg Nyborg Middelfart and Faaborg)	Area III (The rest of the County of Fun
Type of area	City	Towns	Rural
Population density (inhabitants/km²)	553	162	72
No of males	81 805	43 313	94 345
No of females	85 683	45 020	89 590
No of thyrotoxicosis cases 1972–74	22 ♂ 104 ♀	11 ♂ 62 ♀	24 ♂ 141 ♀
Standardized 3-year incidence rate per 100 000[a]	27 7 ♂ 123 1 ♀	24 7 ♂ 132 8 ♀	24 5 ♂ 159 [illegible]

[a] *Standard the total population of the County of Funen*

[b] Standardized normal deviation = 2 01 (0 01 < p < 0 05)

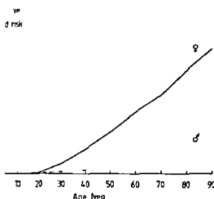


Fig 1 Es ma ed cumulat ve r sk of develop ng thyro- o s

the nc dence rate ris ng progress vely The nc dence rate in women (98 9/100 000) is d in the group aged 70–79 and n men (34 6/ 00) n the group aged 80 and more with a smal eak n the age group 40–49

ble II shows the geographical distribution of otox cos s cases and the general standard zed s for each area in relat on to both sexes It ears that there is a tendency towards a h gher lence of thyrotoxicos s among women n areas a lower degree of urban sation A comparison een area I w th the h ghest and area II w th the st degree of urbanisat on shows a s gn f cant rence (0 01<p<0 05) None of the other d ffer s are s gn f cant

he age spec f c inc dence rates have been used he bas s for calculation of the morbid ty risk e for bo h sexes (Fig 1) In this connect on the b d ty risk at a g ven age is def ned as the risk of lop ng d agnost cally verif ed thyrotox cosis at age before the given one The curves of both s r se evenly w th age showing a total l fe risk bout 5% for women and of about 1% for men the est mated cumulative risk f gures are ed to the age groups of the ent re population of Funen reg on an assessment can be obta ned of pre alence of current and previously d agnosed no longer present hyperthyro d sm The crude t prevalence rate for women can then be as ed as 1 4% and for men as 0 3%

DISCUSSION

rary to earl er stud es the present nvest ga ncludes both in pat ents and patients d ag nosed by phys c ans outside the hosp tal As the latter group const tutes only 11% of the total series we can conclude that new cases of thyrotoxicosis are in general admitted to hosp tal for establ shment of the d agnosis and nst tution of treatment

The val d ty of our data rests primarily on the fact that phys c ans in the reg on under study were aware of the sign f cance of any thyrotox c symp tomatology As t is imposs ble to prov de evi dence for th s on the bas s of the data from our study we have obta ned the number of serum thyrox n tests performed in the study reg on during 1974 Of a total of 16714 tests 14000 are assumed to relate to approximately 10000 persons w th sus pected new thyrotoxicos s and th s d agnosis was established in only 116 cases during 1974 Thus the common use of thyro d funct on tests seems to nd cate that physicians are in fact aware of thyrotox c symptomatology On the other hand it must be presumed that no d agnosis would be made without laboratory conf rmat on and therefore we conclude that our series includes all ne ly diagnosed cases of thyrotox cos s with n the l mits of time and terr tory set for the study

In the present study as in previous ones (6 7 8 10) there is ev dence of a d st nct sex d fference the rat o between overall nc dence rates n women and men be ng approx mately 5 1 (Table I) Th s d fference is repeated in all age groups although it appears to be less pronounced in the youngest and oldest pat en s

Earl er ep dem olog cal stud es have shown an age peak for thyrotox cosis in pat ents aged 0– 0 years Iversen (7) was the f rst to po nt out that this peak has tended to sh ft toward the h gher age groups in the course of th s century Two recent Dan sh stud es (8 10) have shown that elderly pa t ents now const tute a comparat vely large propor tion of newly d agnosed cases of thyrotox cos s In the former of these stud es (8) the majority of pa t ents were older than 60 years Our nvest gat on conf rms that the h ghest inc dence rate has now shifted to those 70 years of age or older

Th s development is probably due to several fac tors Firstly doctors have become more fam l ar w th atyp cal forms of the cond t on espec ally in older patients Secondly d agnostic methods have mproved considerably A d fference in the fre quency of adm ss on to hosp tal w th n the var ous age groups m ght be another factor but th s expla nat on is not supported by our results s nce only

Table III *Incidence rates of thyrotoxicosis in various studies*

Reference	Period	Country	Annual incidence rate per 100 000 ♂	♀	♂ + ♀
Iversen (7)	1938–41	Denmark	5 7	43 6	24 6
Iversen (7)	1942–44	Denmark	24 4	148 3	81 5
Furszyfer et al (6)	1935–67	USA	8 3	36 8	19 8
Thjordleifsson (9)	1938–67	Iceland			17
Thommesen et al (10)	1966	Denmark	8	44	22
Present study	1972–74	Denmark	8 7	46 5	27 6

about 10% of all patients (representing all age groups) had not been admitted to hospital at the time of diagnosis It cannot be ruled out however that the hospitalized patients in earlier studies may have been collected during periods when the admission frequency particularly with regard to the elderly was lower than now

As shown in Table III the overall incidence in our study is identical with that in previous studies The higher occurrence observed in the elderly has not affected materially the size of the overall incidence rate since the elderly represent only a small proportion of the general population The present incidence rate in Denmark is similar to that before the Second World War An epidemic of thyrotoxicosis in Denmark in 1942 and 1943 described by Iversen (7) appears to have been of a temporary nature without lasting effect on the incidence rate

In the Minnesota study (6) a higher incidence of thyrotoxicosis was found among the city population than among the rural yet the authors did not attach any great importance to this finding We found a significantly higher incidence rate among women from areas with a low degree of urbanisation than in the Odense area (city area) This disparity can hardly be ascribed to any difference in medical practice since the standard of medical service in Denmark is very homogeneous and does not differ between urban and rural areas

The cumulative morbidity risk (Fig 1) has been estimated on the assumption that all members of the study population throughout their lives and up to the conclusion of the survey had been exposed to the same age specific morbidity risks Correspondingly for the application of the graphs to future populations it is a presupposition that these conditions are constant A further prerequisite to estimation of the prevalence is the assumption thyrotoxicosis is not associated with an excess tality

Giving these premises it can be concluded the Funen region and presumably in the wh Denmark 1 4% of women and 0 3% of men have had thyrotoxicosis This is not far fro prevalence reported recently from England Tunbridge et al (11) found a prevalence of 1 females and 0 16% in males

REFERENCES

1 Armitage P Statistical methods in medical re Blackwell Scientific Publications Oxford 197

2 Cutler S J & Ederer F J Chronic Dis 8 6 1958

3 Danmarks Statistik Befolkningen i de enkelt muner pr 1 januar 1972 fordelt efter køn ægteskabelig stilling Statistisk Tabelværk 19 Copenhagen 1972

4 — Befolkningen i de enkelte kommuner pr 1 1973 fordelt efter køn alder og ægteskabelig Statistisk Tabelværk 1973 XIII Copenhagen 19

5 — Befolkningen i de enkelte kommuner pr 1 1974 fordelt efter køn alder og ægteskabelig Statistisk Tabelværk 1974 V Copenhagen 19

6 Furszyfer J Kurland L T McConahey Elveback L R Mayo Clin Proc 45 636-644 1

7 Iversen K Temporary rise in the frequ thyrotoxicosis in Denmark 1941–1945 Ros and Bagger Copenhagen 1948

8 Rønnow Jessen V & Kirkegaard C B 41–43 1973

9 Thjordleifsson B Acta Med Scand 19 1975

10 Thommesen N Nirell I & Østergaard H P Ugeskr Laeger 133 1663–1669 1971

11 Tunbridge W M G Evered D C Hall R ton D Brewis M Clark F Grimley Ev Young E Bird T & Smith P A Clin Endo 7 481–493 1977

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The Effect of Beta-Blockade on Glucose Tolerance and Insulin Release in Adult Diabetes

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RACT Blood glucose and plasma insulin levels studied in ten adult diabetics treated in a cross ashion for at least three weeks with alprenolol, selective β blocker, or with metoprolol, a car ctive β_1 blocker Dietary intake was controlled days prior to the study which comprised both d oral glucose tolerance tests Mean fasting glucose levels were significantly higher on al ol than on metoprolol The increase in fasting glucose was particularly pronounced in two ts In these subjects the glucose tolerance fol both an i v and an oral glucose load was d when treatment was switched from meto- to alprenolol Lower plasma insulin levels in se to glucose were also found in these patients renolol than on metoprolol The mean insulin for all ten patients did not differ significantly n the two treatment periods These data show eatment with a non selective β blocker can in patients cause a considerable deterioration of cose tolerance, presumably due to inhibition of 1 release

rds alprenolol metoprolol
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tics run an increased risk of developing var ardiovascular disorders such as ischemic disease (IHD) and hypertension Consequent atment with different agents such as β ad ptor blocking agents or diuretics may be con d It seems quite clear that diuretics may im e diabetic condition (10) as well as lead to a d glucose tolerance in some non-diabetic ensives (2 13) Only few studies on the effect lockade on glucose tolerance have appeared n-diabetic subjects β blockers influence e tolerance only to a small extent or not at all 17) However there are reports of clear re ns in glucose tolerance in some patients (5 18) It appears that there may be differences in this respect between a cardioselective β_1 blocker and a non selective β blocker (18) The reason for this may be the presence of β receptors in human pan creas (19)

It is particularly important however to evaluate the influence of β blockade on blood glucose con trol in diabetics Wright et al (20) reported recently that β blockers may to a small extent raise the blood glucose levels during the day in diabetics There was no significant difference in this respect between a β_1 selective (metoprolol) and a non selective (propranolol) drug although the mean blood glucose levels were lower on metoprolol at all sampling times In order to evaluate the effect of drugs on blood glucose levels it is necessary to control the dietary intake Such a control does not appear to have been done in that study

We have investigated the tolerance to an i v and an oral glucose load in ten adult diabetics while treated in a cross over fashion with metoprolol or a non selective β blocker alprenolol The dietary in take was controlled during three days prior to the glucose tolerance tests

PATIENTS AND METHODS

Ten adult diabetics nine of whom required sulfonylurea treatment were studied Six patients were treated with alprenolol 200 mg b i d and four with metoprolol 100 mg b i d due to IHD Their diabetes was considered well controlled and they had been seen regularly on an out patient basis The clinical characteristics of the patients are shown in Table I The alprenolol and metoprolol doses given are considered to give equipotent blockade of the β receptors (2 11)

The patients were given an isocaloric formula diet con taining 16% protein 45% carbohydrate and 39% fat in

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Table I *Cl nical cl aracteristics of the diabet cs stu l ed*

Pat no	Age (y)	Sex	B wt (kg)	Known durat on of IHD (y)	Duration of d abetes (y)	Therapy bes des β blockers
1	50	♂	85	[illegible]	1	Gl benclam de [illegible] 5 mg × 1
2	56	♂	90	4	3	Chlorpropam de 250 mg × 1
3	65	♂	75	13	6	Chlorpropam de [illegible]50 mg × 1
4	65	♂	73	7	15	Chlorpropam de [illegible]50 mg × 1
5	61	♂	106	9	6	Chlorpropam de 250 mg × 1 me f[illegible]
6	7[illegible]	♂	73	6	6	Gl benclamide 5 mg × 1
7	60	♂	84	10	3	Chlorpropam de [illegible]50 mg × 1
8	48	♂	122	2	1	D et
9	58	♀	86	11	[illegible]	Chlorpropam de 37[illegible] mg × 1 metfo[illegible] 0 5 g × [illegible]
10	54	♂	96	4	3	Tolbutam de 0 5 g × [illegible]

prewe ghed ndiv dual port ons to be taken three t mes da ly at mealtime for three days prior to the glucose tol erance tests The pat ents came to the laboratory in the morn ng after an overn ght fast They had taken the r last alprenolol or metoprolol dose one hour before the glucose tolerance tests Venous blood samples were drawn for the analysis of blood glucose us ng a gluco e ox dase techn que and plasma insul n levels (Phadebas Phar macia Uppsala Sweden) I v glucose (0 5 g/kg b wt) was then injected rap dly and venous blood samples were drawn at the ind cated t mes On the next day the pat ents came aga n to the laboratory and an oral glucose tolerance test (100 g glucose d ssolved in [illegible]00 ml water) was per formed under the same cond t ons

After the tolerance tests the pat ents were switched to the other β blocker (i e alprenolol nstead of metoprolol and v ce versa) and the st dy was repeated n an analogous way after a treatment period of at least three weeks Any other concom tant med cat on was continued unchanged throughout the study

RESULTS

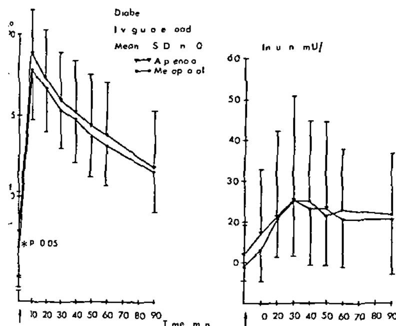
I v gl icose tolerance

Table II shows the individual fasting bloo levels before the i v and oral gluco e t tests Most patients (7 and 6 of 10 respecti higher glucose levels on alprenolol than prolol although the values did not genera markedly Pat ents 9 and 10 however s derably h gher fasting levels on alpren ble II)

There was no s gn f cant d fference in me glucose levels reached during the i v toler although all values were somewhat h ghe prenolol (Fig 1) The mean insul n level and during the glucose load are also dep te 1 It is clear that there were great interin

Table II *Fasting blood gli cose (mM) in 10 d abetic subjects after at least 3 eeks treatm alprenolol or metoprolol*

Pat no	Before i v test		Before oral load	
	Alprenolol	Metoprolol	Alprenolol	Metoprolol
1	7 2	7 0	6 8	5 6
2	6 9	5 0	6 3	3 5
3	10 5	11 1	10 2	12 0
4	7 2	7 5	8 5	7 1
5	5 7	5 4	5 8	5 8
6	6 3	6 0	7 3	7 8
7	3 8	4 3	3 4	3 6
8	8 9	8 0	9 1	8 9
9	11 0	8 1	11 0	7 3
10	10 8	6 9	10 8	6 6
Mean ± S D	7 8 ± [illegible] 4	6 9 ± 1 9	7 9 ± 2 4	6 8 ± [illegible] 5
	$p < 0\ 05$		$0\ 05 < p < 0\ 1$	



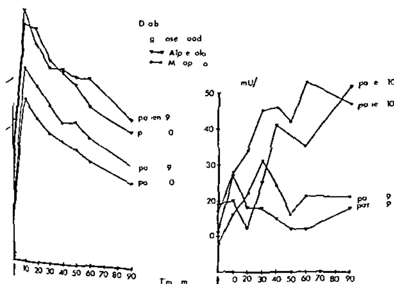
F g 1 Glucose and nsul n level n respon e to an i v glucose load (0 5 g/kg b wt) n 10 adult d abet cs trea ed with alprenolol or metoprolol for at least three weeks

ences and no s gnificant change was found en the two drugs

glucose tolerance of pat ents 9 and 10 whose g blood glucose levels were cons derably ed by alprenolol (Table II) was analysed ately As shown in F g 2 the r glucose tol e was cons derably reduced by alprenolol and as assoc ated w th a reduced insul n release g the load

Oral gl cose tolerance

Essent ally similar results were obtained as with the i v tolerance test The fast ng blood glucose levels were generally h gher on alprenolol (Table II) The insul n response to glucose was not s gnif cantly different but again the insul n levels were lower on alprenolol in pat ents 9 and 10 and this was as soc ated with higher blood glucose levels during the tolerance test (Fig 3)



F g 2 Glucose and insulin le els in response to an i v glucose load n patients 9 and 10 t eated w th alprenolol or metoprolol for at least three weeks

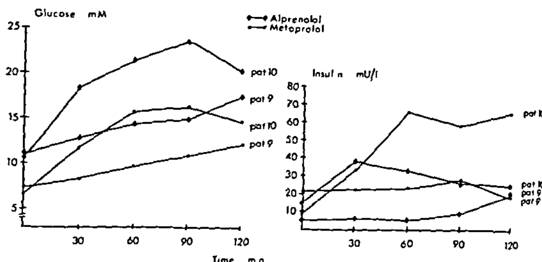


Fig 3 *Glucose and insulin levels in response to an oral* glucose load (100 g) in patients 9 and 10 treated with alprenolol or metoprolol for at least three weeks

DISCUSSION

In a recent study it was shown that stimulation of β_2 receptors leads to insulin release in man (19) However the importance of the β receptor for glucose-stimulated insulin release is not clear although an association is suggested by the observation that glucose stimulated insulin release is greatly augmented by simultaneous β receptor stimulation (7) Also significant changes in insulin release after β blockade in non-diabetics were not noted in some studies (8 9 17) but were found in some others (5 18) The reason for this may be that adrenergic mediated insulin release is of quantitative importance in some patients Cerasi et al (4) for instance found a clear reduction in insulin release in some patients while their other patients were unaffected The consensus that insulin release may be reduced by non selective β blockade in some patients is also exemplified by the fact that patients with insulinoma can be successfully treated with propranolol (3) Other studies have shown that sulfonylurea stimulated insulin release may also be reduced by β-blockade (14 15)

The present investigation was designed to study the influence of β-blockade on glucose control in diabetics In order to eliminate effects of possible changes in the diet caloric intake was controlled for three days prior to the study The data show that the non selective β-blocker alprenolol raised the fasting glucose levels slightly in most patients but this effect was pronounced in two of patients The deterioration in glucose to these patients seems to be due to a low release In these patients then β media release appears to be of quantitative m Neither from a clinical point of view nor mode of medication were there any app ferences between these two patients and t It is of course also feasible that blocka β receptors leads to an unopposed α stim catecholamines thereby inhibiting insul (16) Further studies are required to d point

Irrespective of the mechanisms involv pears that a non selective β blocker in c administered clinical doses influences gl erance in adult diabetics to a greater exte cardioselective β_1 blocker

Since cardioselective β_1 blockers not o ence glucose tolerance less but also an potentially hazardous complication of the state namely recovery from hypoglycemi it appears that these agents are preferable beta blocker is required in diabetics

REFERENCES

1 Åblad B Johnsson G Norrby A & S Potency and time-effect relationship ranolol and H 56/28—Comparative s

administration Acta Pharmacol Toxicol (Suppl 2) 25 85 1967

Amery A Berthaux P Bulpitt C Deruyttere M de Schaepdryver A Dollery C Fagard R Foret e F Hellemans J Lund Johansen P Mutsers A & Tuomilehto J Glucose intolerance during diuretic therapy Results of trial by the European working party on hypertension in the elderly Lancet 1 681 1978

Blum I Doron M Laron Z & Atsmon A Pre ention of hypoglycemic attacks by propranolol in a patient suffering from insulinoma Diabetes 24 535 1975

Cerasi E Efendic S & Luft R Role of adrenergic receptors in glucose-induced insulin secretion in man Lancet 2 301 1969

Cerasi E Luft R & Efendic S Effect of adrener ic blocking agents on insulin response to glucose nfusion in man Acta Endocr (Kbh) 69 335 1972

Deacon S P Karunanayake A & Barnett D cebutolol atenolol and propranolol and metabolic sponses to acute hypoglycaemia in diabetics Br Med J 2 1255 1977

eckert T Lauridsen U B Madsen S N & eckert M Serum insulin following isoprenaline in ormal and diabetic persons Horm Metab Res 4 229 1972

Åberg G & Hansson B -G Glucose tolerance and insulin release in hypertensive patients treated with e cardioselective β receptor blocking agent meto- l Acta Med Scand 202 393 1977

edstrand H & Åberg H Insulin response to in travenous glucose during long term treatment with propranolol Acta Med Scand 196 39 1974

oward B E The treatment of hypertension with lorthalidone a long acting diuretic agent Curr her Res 7 304 1965

11 Johnsson G Nyberg G & Solvell L Influence of metoprolol and propranolol on hemodynamic effects induced by physical work and isoprenaline Acta Pharmacol Toxicol (Suppl 5) 36 69 1975

12 Lager I Blohme G & Smith U Effect of car dioselective and non selective β blockade on the hypoglycaemic response in insulin dependent di abetics Lancet I 458 1979

13 Lewis P J Kohner E M Petrie A & Dollery C T Deterioration of glucose tolerance in hypertensive patients on prolonged diuretic treatment Lancet I 564 1976

14 Massara F Strumia E Camanni F & Molinatti G M Depressed tolbutamide induced insulin re sponse in subjects treated with propranolol Dia betologia 7 287 1971

15 Podolsky S & Pattavina C G Hyperosmolar non ketotic diabetic coma A complication of propranolol therapy Metabolism 22 685 1973

16 Porte D Jr & Robertson R P Control of insulin secretion by catecholamines stress and the sym pathetic nervous system Fed Proc 32 1792 1973

17 Vedin A Wilhelmsson C & Bjorntorp P Induc tion of diabetes and oral glucose tolerance tests during and after chronic β blockade Acta Med Scand (Suppl) 575 37 1975

18 Waal Manning H J Metabolic effect of β adre noceptor blockers Drugs (Suppl) 11 121 1976

19 William-Olsson T Fellenius E Bjorntorp P & Smith U Differences in metabolic responses to β adrenergic stimulation after propranolol or metoprolol administration Acta Med Scand 205 201 1979

20 Wright A D Barber S G Kendall M J & Poole P H Beta adrenoceptor blocking drugs and blood sugar control in diabetes mellitus Br Med J 1 159 1979

Castle's Test (with Vitamin B_{12} and Normal Gastric Juice) in the Ileum in Patients with Genuine and Patients with Tapeworm Pernicious Anaemia

Bertel von Bonsdorff and Ruben Gordin

From the IVth Department of Medicine University of Helsinki Helsinki Finland

TRACT A mixture of vitamin B_{12} and normal ic juice, instilled through an intestinal tube into eum produces haematological remission in pa with tapeworm pernicious anaemia When a ir mixture is administered by mouth this effect to occur This observation constitutes evidence our of the view that Diphyllobothrium latum ted to the proximal portion (jejunum) of the ine, absorbs the vitamin B_{12} contained in the thus preventing vitamin bound to the intrinsic of the gastric juice from reaching the receptors distal portions of the small intestine of the host nuine pernicious anaemia remission results the administration of vitamin B_{12}+gastric juice by mouth and into the ileum

ords Diphyllobothrium latum pernicious anaemia n B_{12} absorption

Med Scand 208 193 1980

monograph published in 1977 (4) (below refer as D monograph) the kinetics of vitamin B_{12} n tapeworm pernicious anaemia (PA) and the genesis of this disease are discussed The graph represents a recapitulation of investiga on this problem complex which for the part of team of workers were concluded about 1960 present paper is an addendum to the mono-

ring 1949–54 we performed Castle s test with nd normal human gastric juice (GJ) intro- l into the ileum by intestinal intubation in 4 of genuine PA and 13 of tapeworm PA The were discontinued when radioactive B_{12} be available and it was considered more impor to study D latum infection by the isotope ique At about the same time we moreover ne interested in the microbiological determina of B_{12} in the blood and in the parasite The reports of the above mentioned experiments were put aside and finally fell into oblivion They have recently been found again and the results seem valuable enough for publication

METHODS

One of us has described intestinal intubation of D latum carriers for the demonstration of tapeworm ova in the intestinal contents (2) The distance from the mouth to the level where tapeworm ova were found was 130–135 cm (mean 170) in 11 cases of D latum infection without anaemia 95–135 cm (mean 115) in 11 cases of manifest tapeworm PA The distance from the mouth to the duodenojejunal flexure was estimated at 70–80 cm to the junction between the jejunum and the ileum at 140–150 cm and to the ileo caecal valve at 250–300 cm

In the experiments to be described below the same principles as in oral administration of Castle s test were applied After intubation to a level of 145–200 cm a mix ture of 5 µg B_{12} and 100 ml depepsinized GJ daily was instilled through the tube in 8-day periods Parallel tests were performed without GJ with 5 µg of B_{12} diluted in 100 ml of water The position of the tube was radiologically checked Other measures appear in the diagrams

RESULTS

Genuine PA

A good haematological response was obtained in all 4 cases in this group A typical course is shown in Fig 1 At a level of 145 cm B_{12} + GJ gave remission and a stronger reticulocytosis than the same mix ture administered by mouth during a subsequent test period An identical result was obtained (at 165 cm) when 5 ml of an injectable liver preparation (Heptomin®) was used instead of pure B_{12} Fig 2

Abbreviations B_{12} = vitamin B_{12} PA = pernicious anaemia GJ = gastric juice IF = intrinsic factor

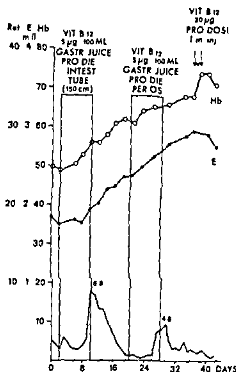


Fig 1 Genuine PA Woman 54 years *E* = erythrocytes (mill /mm³) 100% Hb corresponds to about 14 g/ml *Ret* = reticulocytes (% of *E*)

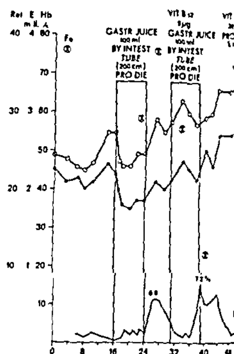


Fig 2 Genuine PA Man 72 years

shows an experiment in which 100 ml GJ alone was instilled (at 200 cm) during the initial period Definite reticulocytosis and haematological remission ensued However the effect was stronger during the second trial period when GJ was given in combination with B_{12} The fourth patient in this group received 100 ml GJ daily by mouth during the first trial period with no result B_{12} + GJ administered after intubation (200 cm) produced a good remission (maximum reticulocytosis 13 3%)

Tapeworm PA

Rapid remission resulted in 4 cases after instillation of B_{12}+GJ into the ileum (at 150 cm) Two experiments are reproduced in Figs 3 and 4

The effect of B_{12} alone administered first into the ileum and subsequently by mouth was studied in 9 cases The results were as follows

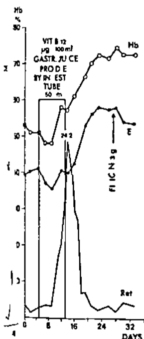
A) Instillation into the ileum caused reticulocytosis and moderate or no improvement of the blood values (Hb E) (*a*) Administration by mouth (one case Fig 5) resulted in marked remission (*b*) Administration by mouth (5 cases) produced no remission One case is illustrated in Fig 6 In another case (Fig 7) a weak reticulocytosis without remission was observed B mouth had no effect either Two blood tr had a slight influence on the curves

B) Instillation into the ileum failed to pr reticulocytosis The blood values dropped ministration by mouth was followed ulocytosis (7 2%) and moderate remis case) (*b*) Administration by mouth re neither reticulocytosis nor any improveme blood values (2 cases) In one case Bend commercial preparation of B_{12} and pig in tor (IF) then commonly used) given for fore expulsion of the worm produced mission as was usually the case in both PA and genuine PA

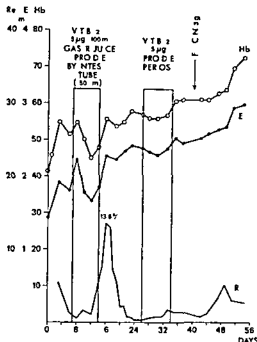
DISCUSSION

Genuine PA

In the early 50s it was not yet clearly es where the absorption of B_{12} takes place above mentioned study of 4 cases we our knowledge the first to show that sorbed in the ileum in the presence of results were shortly mentioned at Europaisches Symposium uber Vitamin B strinsic Factor in May 1956 (1) Later



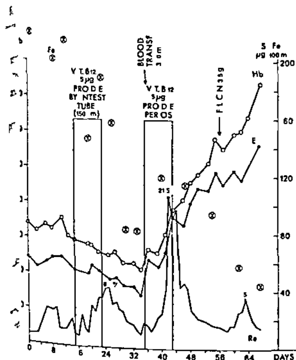
Tapeworm PA Woman 45 years I v insul n test 19 total ac d ty 73



F g 4 Tapeworm PA Woman 38 years Insul n test not made

ed shed that the B absorption is princ pally ted by receptors located in the distal port on leum The problem is discussed in the D graph (4) p 145

In one case GJ w thout any B_{12} adm n stered at a level of 200 cm produced a submax mal haematolog cal response (F g 7) A sim lar effect was never obta ned w th GJ alone by mouth Obv



F g 5 Tapeworm PA Woman 0 years I v nsul n test free HCl 27 total ac d ty 45

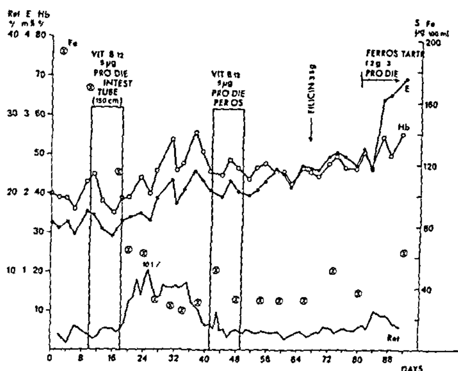


Fig 6 Tapew
Woman 6 ye
hydria

ously the remission in this case was due to the presence of small amounts of B_{12} in the ileum either derived from the food or synthetized in the distal portion of the small intestine

Tapeworm PA

Castle s classical test administered by mouth fails to produce remission in tapeworm PA However in those 4 cases in whom we instilled B_1 + GJ into the ileum reticulocytosis and blood remission oc curred For the sake of control oral administration of B_1 ought to have preceded the instillation into the ileum in at least one experiment On the other hand the failure of Castle s classical test in tapeworm PA may be considered an established fact on a basis of a very large number of previous experiments (3 5) (Fig 7)

In contrast to genuine PA the endogenous pro duction of IF has not ceased in tapeworm PA (D monograph (4) pp 135 170–173) The effect of B_{12} without any addition of GJ has therefore been tested in tapeworm PA Orally administered B_1 alone gave either no haematological response or a remarkably good remission (5) These results are discussed in the D monograph p 146

The instillation of B_1 alone into the ileum in tapeworm PA gave variable results In some cases unused IF seems to have been present in the ileum in other cases not When the IF–B_{12} complex is exposed to the action of D latum in the i tine and the B_1 is absorbed by the wor component is obviously split off and m Even under normal conditions the surplus

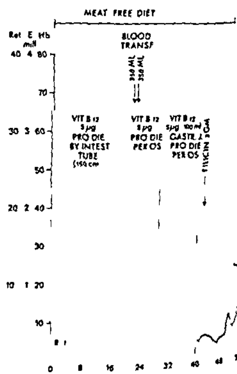


Fig 7 Tapeworm PA Woman 76 years A

obably degraded during its passage through the tinal canal (D monograph p 161) though in cases small amounts apparently get as far as eum

cording to our theory of the pathogenesis of worm PA the disease originates from a com on between the host and the parasite for the ontained in the food Among the circumstances red for the development of tapeworm PA onograph pp 175–178) the situation of the in the small intestine is of decisive impor The higher up in the jejunum the parasite has ne attached the greater the risk that it will e for itself the B_{12} that the host organism is in of The evidence in favour of this theory is In the D monograph (p 163) a test program lined which would further elucidate the ques

ing tests (radioactive B_{12} + GJ) or plasma vitamin bioactivity tests performed by instillation of the test hrough an intestinal tube into the duodenum and (in me person) into the ileum respectively with the r in situ in D latum carriers—both with and without th ia—would be of interest A greater absorption from the ileum would lend further support to the theory set forth above

However the most essential points of the prob lem have been clarified by the experiments reported above performed by an earlier more laborious technique The most important issue is the finding that remission results in tapeworm PA if B_{12} + GJ are administered into the ileum and tapeworm situated higher up in the intestine is thus prevented from interfering These phenomena could no doubt be elucidated in greater detail utilizing the isotope technique but it may be questioned whether the gain would be worth the trouble considering the insight already acquired

REFERENCES

1 v Bonsdorff B 1 Europaisches Symposion uber Vitamin B_{12} und Intrinsic Factor in Hamburg 23–26 Mai 1956 p 311 Enke Stuttgart 1957
2 — Acta Med Scand 129 213 1947
3 — Acta Med Scand (Suppl) 196 456 1947
4 — Diphyllobothriasis in man Academic Press London 1977
5 v Bonsdorff B & Gordin R Acta Med Scand (Suppl) 259 112 1951

Acta Med Scand ?08 199 ?03 1980

The Relation between the Levels of HDL Cholesterol and the Capacity for Removal of Triglycerides

Jostein Sauar Sverre Skrede Jan Erikssen and Jan P Blomhoff

From Med cal Dep rtments A and B and Inst t te of Cl n cal B ocl em stry R ksl osp talet Osl Nor a

RACT In twenty two men with normal ...s clinically by exercise ECG and laboratory ...e performed an i v fat tolerance test meas ...nt of LCAT activity and the activities of post ...n triglyceride lipases and estimated serum HDL cholesterol was positively correlated to ...tein l pase (r 0 50 $p<0\ 05$) and to the frac removal rate of exogenous fat (r-0 59 ...l) and negatively to the fasting levels of tri ...des (r -0 65 $p<0\ 01$) LCAT was neither ...ted to HDL cholesterol nor to the fat removal ...Our results confirm that a high triglyceride ...al capacity is closely correlated to a high level ...L The association between the catabolism of ...ende rich lipoproteins and HDL was thus ...r substantiated

...rds h gh dens ty l poprote ns l poprote n l pase ...ride removal capac ty

...ed Scand ?08 199 1980

...l stud es have suggested that high concentra ...f h gh density l poprotein (HDL) may have a ...t ve role against coronary atherosclerosis (7

The mechanism involved is unknown but it ...en postulated that HDL/lecithin cholesterol ...nsferase (LCAT) may remove cholesterol ...he arterial wall (11) or that HDL may prevent ...of cholesterol rich l poprote ns (6)

...L s synthesized and secreted by the liver (15) ...e ntest ne (14) A close negative relation ...en very low density l poprotein (VLDL) ...ol sm and HDL exists This is reflected by a ...ve correlation between plasma triglyceride ...ntrat on and HDL both in normal subjects and ...tents w th hyperl poproteinemia (18) A posi ...orrelat on between HDL cholesterol and ...se t ssue l poprotein lipase has recently been ...ed by Nikkila et al (25) Eisenberg (8) has ...ocused upon l poprotein l pase as the link between VLDL and HDL A positive correlation between HDL and the removal rate of intravenously administered fat has recently been reported (17)

In order to elucidate further the relationship between triglyceride catabol sm and HDL concentration in plasma we stud ed lipoprotein l pase act vity in postheparin plasma and the fract onal removal rate of an exogenous lipid in relation to HDL cholesterol in healthy male subjects

SUBJECTS AND METHODS

In 197?-75 ?014 apparently healthy male employees (aged 40-59 years) from five major compan es/governmental agenc es in Oslo Norway part pated in a card ovascular survey (9) In 19 6 63 of the 183? subjects def ned as normals in that survey were reexam ned cl n cally by exercise ECG and serum l p d analyses Two of the 63 (both with low HDL cholesterol) had suffered a myocard al nfarction s nce the primary survey and were excluded None of the others had symptoms or s gns of coronary heart d sease (CHD) Twenty two of the rema n ng 61 normals were selected for the present study (performed in 1977 ?8) represent ng the 11 h ghest group I mean age 53 years) and 11 lowest (group II mean age 5? years) levels of HDL cholesterol n 1976 No d fferen e in hab tual phys cal act v ty alcohol consumpt on or smok ing hab ts was found between the two groups Fast ng blood glu ose and insul n were w th n the reference range n all subjects stud ed None had hypertension and none was on l p d lower ng d ets or drugs None of the subjects

The present data have been presented at the Åkarp Meet ng on HDL in Aug 1978 (ref 30)

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Abbre at ons HDL h gh dens ty l poprote n LDL low dens ty l poprote n VLDL very low dens ty l poprote n LCAT lecit n cholesterol acyltransferase LCAT S N LCAT accord ng to Stokke & Norum LCAT G W LCAT accord ng to Glomset & Wright CHD = coronary heart d sease

Table I *Plasma lipids Intralipid removal and activities of lipases and LCAT in groups I and II*
Group I = 11 men with mean HDL cholesterol level of 1 77 mmol/l (S D 0 23) group II = 11 men with
cholesterol level of 1 09 mmol/l (S D 0 19)

	Group I		Group II	
	Mean	S D	Mean	S D
Total cholesterol (mmol/l)	5 9	1 1	5 0	0 8
Triglycerides (mmol/l)	0 7	0 3	1 4	0 5
Intralipid removal (%/min)	3 4	1 2	2 1	0 8*
Lipoprotein lipase (µmol FFA/ml plasma/h)	*14 4*	*4 3*	*10 8*	*3 1**
Hepatic lipase	21 0	6 6	25 8	7 8
LCAT S N (µmol/l/h)	53	10	64	19
LCAT G W (µmol/l/h)	111	22	119	25

*$p<0.05$ **$p<0.01$ for lack of significance of difference between the groups calculated by Student s t test

had symptoms of CHD but exercise ECG showed ischemia in two group II subjects

Blood sampling and investigations related to triglyceride catabolism were performed in the morning after 12–14 hours fast and after 15 min rest with the subjects in prone position The subjects were on their ordinary diet They were told not to drink alcohol on the day before the examination Since the previous survey showed that alcohol consumption took place mainly during the weekends (10) the investigations were performed in the middle of the week Heparin was injected for subsequent analyses of plasma lipoprotein lipase activity on the day after measurement of the removal rate of an exogenous lipid load

Triglyceride removal capacity was measured as described by Nikkila et al (24) by i v infusion for 10 min of 20% Intralipid® (Vitrum Sweden) 0 1 g/kg b wt The T½ of Intralipid disappearance was calculated from the linear slope of the curve obtained from serum triglyceride measurements at 10 15 20 25 and 30 min after the end of the infusion and was plotted against time in a semilogarithmic plot

Lipase activity was assayed in plasma samples drawn 15 min after i v administration of heparin 100 U/kg b wt (29) Lipoprotein lipase and hepatic lipase activity were determined by the immunoprecipitation method described by Huttunen et al (16) After preincubation with specific antiserum against hepatic lipase the lipoprotein lipase activity in an artificial substrate of triolein was tested as the remaining triglyceride lipase activity at 0 1 M NaCl in the presence of serum as cofactor source

Total cholesterol and triglycerides were me[asured by] methods adapted for AutoAnalyzer (10) HDL c[holesterol] was estimated by an enzymatic method (?) a[fter precipi]tation of VLDL and LDL with heparin and ma[nganese] Analyses of free cholesterol were performed by [gas] chromatography (3) LCAT activity was me[asured ac]cording to Stokke and Norum (31) (LCAT [S N) and] Glomset and Wright (13) (LCAT G W) Heat[ed] plasma from one healthy subject served as [a] substrate source for LCAT G W analyses

Spearman s rank correlation test and Stude[nt s] were used for statistical analyses

RESULTS

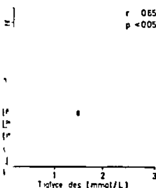
The level of HDL cholesterol present in [sub]jects examined was significantly correla[ted with the] level found at examination of stored sera [samples] drawn 3–6 years ago ($r=0.61$ $p<0.01$) an[d] drawn and assayed one year ago ($r=0.88$ p

Table I shows that total cholesterol [trigly]cerides the Intralipid removal rate and lip[oprotein] lipase activity were significantly different [in groups] I and II Only one subject had a serum trig[lyceride] level higher than 1 7 mmol/l (2 3 mmol/l) [...] total cholesterol levels were within the n[ormal] range in all (i e ≤7 5 mmol/l) The diff[...]

Table II *Correlation matrices between triglycerides Intralipid removal lipase and LCAT activ[ities]*

	Triglycerides	Lipoprotein lipase	Hepatic lipase	Intralipid removal	LCAT G
Lipoprotein lipase	−0 56				
Hepatic lipase	0 28	0 17			
Intralipid removal	−0 71 *	0 28	−0 48		
LCAT G W	0 42	−0 37	0 02	−0 25	
LCAT S N	0 81	−0 27	0 15	−0 17	0 5[?]

* $p<0.05$ ** $p<0.01$ * $p<0.001$ calculated by Spearman s rank correlation test



... 1 Comparison of plasma triglycerides and HDL ...sterol level

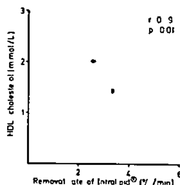


Fig 2 Removal rate of Intralipid® in relation to HDL cholesterol level

level in the two groups caused almost the ...e difference in total cholesterol levels

...e triglyceride concentration was inversely cor...ted to lipoprotein lipase activity and to the re...l rate of an exogenous fat load but positively ...lated to LCAT activity (Table II) There was ...ignificant relationship between triglycerides ...hepatic lipase activity The fat removal rate ...negatively correlated to hepatic lipase activity ...not to lipoprotein lipase activity (Table II)

...e concentration of HDL cholesterol was nega...y correlated to triglycerides (Fig 1) but posi...y to the removal rate of Intralipid® (Fig 2) and ...ctivity of lipoprotein lipase (Fig 3) There was ...ignificant relationship between HDL choles... and hepatic lipase activity ($r=-0.33$) or ...T activity ($r=-0.17$ for LCAT S-N $r=0.07$ ...CAT G-W)

DISCUSSION

...emiological studies have suggested that HDL ...be of significance for the pathogenesis of ...osclerosis (7 18 21) The regulation of forma... and catabolism of these lipoproteins is how... only incompletely understood (21) The pres... investigation of essentially normolipidemic ...le aged men has confirmed a close relationship ...een the concentration of HDL cholesterol and ...ctivity of lipoprotein lipase (21 25) and also the ...val capacity of exogenous lipids (17) Our find...are compatible with the formation of HDL in ...na through catabolism of triglyceride rich ...roteins The results agree well with recent re...s by Nikkila et al (21 25) on the relation between HDL and adipose tissue lipoprotein lipase and may at least partly explain the inverse relation between the concentration of plasma triglycerides and HDL which has been found also in other studies (18 22) The importance of catabolism of VLDL (or chylomicron (32)) by lipoprotein lipase as a regulating factor for HDL concentration is also supported by in vitro studies by Nikkila (23) and Eisenberg (8) and by reports on rather low HDL concentration in patients with type I hyperlipoproteinemia or familial LCAT deficiency (lipoprotein lipase activity is low also in the latter condition (4))

The studies by Glomset et al (12) in patients with familial LCAT deficiency have demonstrated a key role of LCAT in lipoprotein metabolism The preferred substrate for this enzyme is HDL (11) In the present investigation no significant relation between LCAT activity and HDL cholesterol was

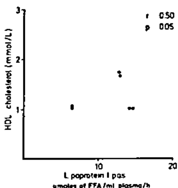


Fig 3 Comparison of lipoprotein lipase activity and HDL cholesterol level

found However this is not necessarily in contrast with the suggestion by Glomset (11) that LCAT is important for removal of cholesterol from cells Important functions of this enzyme in lipoprotein catabolism and cholesterol transport may not be reflected by the total in vitro capacity for plasma cholesterol esterification measured by the two methods used in this study The strong positive correlation between plasma triglycerides and LCAT—also observed previously (1)—might be explained by a concomitant secretion of LCAT and VLDL by the liver as suggested by Nordby (26)

Men who are physically active during their leisure time may have a reduced risk of coronary atherosclerosis (20 33) increased HDL levels lipoprotein lipase activity (22) and removal rate of exogenous lipids (2 17) All these features are in contrast to uncontrolled insulin dependent diabetes (22 24) On this background our results support the concept that a high triglyceride removal capacity is another marker for individuals at low risk for CHD even though VLDL may not be a separate risk factor (7)

REFERENCES

1 Akanuma Y Kuzuya T Hayashi M Ide T & Kuzuya N Positive correlation of serum lecithin cholesterol acyltransferase activity with relative body weight Eur J Clin Invest 3 136 1973

2 Altekruse E B & Wilmore J H Changes in blood chemistries following a controlled exercise program J Occup Med 15 110 1973

3 Blomhoff J P In vitro determination of lecithin cholesterol acyltransferase in plasma Scand J Clin Lab Invest (Suppl) 137 35 1974

4 Blomhoff J P Holme R Sauar J & Gjone E Familial lecithin cholesterol acyltransferase deficiency Further studies on plasma lipoproteins and plasma postheparin lipase activity of a patient with normal renal function Scand J Clin Lab Invest (Suppl) 150 177 1978

5 Burstein M Scholnick H R & Morfin R Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions J Lipid Res 11 583 1970

6 Carew T E Koschinsky T Hayes S B & Steinberg D A mechanism by which high density lipoproteins may slow the atherogenic process Lancet 1 1315 1976

7 Castelli W Doyle J T Gordon T Hames C G Hjortland M Hulley S B Kagan A & Zukel W J HDL cholesterol levels in coronary heart disease a cooperative lipoprotein phenotyping study Circulation 52 97 1975

8 Eisenberg S Structure function rela[tionships in] lipoprotein metabolism In Prot[i]des of the b[iological] fluids (ed H Peeters) 25 135 1978

9 Eriksssen J Rasmussen K Forfang K [&] stein O Exercise ECG and case history in [diag]nosis of latent coronary heart disease amo[ng pre]sumably healthy middle aged men Eur J Ca[rdiol] 6 463 1977

10 Erikssen J & Skrede S Serum lipids a[nd] coronary insufficiency Scand J Clin Lab [Invest] 37 243 1977

11 Glomset J A The plasma lecithin chole[sterol acyl]transferase reaction J Lipid Res 9 155 1968

12 Glomset J A Norum K R Nichol A V W C Mitchell C D Appelgate K R Gorj & Gjone E Plasma lipoproteins in familial le[cithin] cholesterol acyltransferase deficiency Ef[fects of] dietary manipulation Scand J Clin Lab In[vest] 142 3 1975

13 Glomset J A & Wright J L Some propert[ies of the] cholesterol esterifying enzyme in human p[lasma] Biochim Biophys Acta 89 266 1964

14 Green P H R Tall A R & Glickman R M [Rat] intestine secretes discoid high density lipo[protein] Clin Invest 61 528 1978

15 Hamilton R L Williams M C Fielding C J Havel R J Discoidal bilayer structure of [nascent] high density lipoproteins from perfused rat li[ver] Clin Invest 58 667 1976

16 Huttunen J K Ehnholm C Kinnunen P Nikkila E A An immunochemical method for selective measurement of two triglyceride l[ipases in] human postheparin plasma Clin Chim Acta 1975

17 Lisch H J Sailer S & Braunsteiner H B[eziehungen] zwischen der Plasmakonzentration der Lipo[proteine] hoher Dichte (HDL) und der intrav[enösen Fett]toleranz bei Normo-und Hypertriglyzeri[dämie] Klin Wochenschr 56 797 1978

18 Miller G J & Miller N E Plasma high [density] lipoprotein concentration and development of [is]chaemic heart disease Lancet 1 16 1975

19 Miller N E Thelle D S Forde O H & M[jøs O] D The Tromsø heart study High density lipo[protein] and coronary heart disease a prospective c[ase con]trol study Lancet 1 965 1977

20 Morris J N Adam C Chave S P W Su[therland] Epstein L Vigorous exercise in leisure time [and the] incidence of coronary heart-disease Lancet 1973

21 Nikkilä E A Metabolic regulation of plasma [high] density lipoprotein concentrations Eur J Cl[in Invest] 8 111 1978

22 — Metabolic and endocrine control of plasm[a high] density lipoprotein concentration Re[lation to me]tabolism of triglyceride rich lipoproteins [and high] density lipoproteins and atherosclerosis [(ed A M] Gotto Jr N E Miller & M F O[liver]) Elsevier/North Holland Biomedical Pres[s, Amster]dam 1978

23 — Studies on the lipid protein relationships [in normal] and pathological sera and the effects of hep[arin]

erum lipoproteins Scand J Clin Lab Invest (Suppl) t 1953

...ikkila E A Huttunen J K & Ehnholm C Post-heparin plasma lipoprotein lipase and hepatic lipase in diabetes mellitus Relationship to plasma triglyceride metabolism Diabetes 26 11 1977

...ikkila E A Taskinen M R & Kekki M Relation of plasma high-density lipoprotein cholesterol to lipoprotein lipase activity in adipose tissue and skeletal muscle of man Atherosclerosis 29 497 ...978

...ordby G Secretion of lipids and lecithin cholesterol acyltransferase from isolated rat hepatocytes ... Protides of biological fluids (ed H Peeters) ... 709 1978

...hoads G Gulbrandsen C L & Kagan A Serum lipoproteins and coronary heart disease in the population study of Hawaii Japanese men N Engl J Med ...4 793 1976

28 Roschlau P Bernt E & Gruber W Enzymatische Bestimmung des Gesamt Cholesterins im Serum Z Klin Chem Klin Biochem 1? 403 1974

29 Sauar J Skrede S & Blomhoff J P Hepatic lipase and lipoprotein lipase in postheparin plasma in liver disease Relations to plasma proteins Clin Chim Acta 84 213 1978

30 Sauar J Skrede S Eriksen J & Blomhoff J P Triglyceride removal capacity in individuals with high respectively low HDL levels In The Åkarp Meeting on HDL (ed A Gustafson) pp 18–19 Ekstrands Tryckeri Lund 1979

31 Stokke K T & Norum K R Determination of lecithin cholesterol acyltransferase in human blood plasma Scand J Clin Lab Invest 27 21 1971

32 Tall A R & Small D M Plasma high-density lipoproteins N Engl J Med 229 1232 1978

33 Tibblin G & Wilhelmsen L Fysisk aktivitet och risk för hjartinfarkt Lakartidningen 72 343 1975

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HDL-Increasing Effect of Cyclofenil

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TRACT Nineteen patients with low levels of as measured by APO AI have been treated with fenil (a non steroid stilboestrol isomer with very oestrogenic effects) as the only form of therapy therapy elicited a highly significant rise of about in HDL levels A slight increase in transases occurred in 6 patients but was reversible out terminating therapy

words lipoproteins HDL, cresols cyclofenil ar clerosis coronary disease preventive medicine

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cent years a growing body of research has n that there is a very strong negative correla between the plasma HDL (high density lipopro- level and the probability of developing a heart k (6 13 17) The evidence comes both from miological studies in which decreased con ations of plasma HDL have been linked with creased extent of coronary artery occlusion peripheral artery disease (3) and risk of heart k (9) and from in vitro studies in which HDL een shown to influence uptake and release of ar cholesterol (4 16) The relationship seems old both for HDL cholesterol and HDL poproteins AI (APO AI) (3 6 9) and AII (3) ral factors such as oestrogens (11) exercise nd alcohol (10) influence the HDL level It is fore of interest to find ways of elevating the a HDL level in order to study whether this enable us to decrease or eliminate the in ed risk for arterial disease and heart attack ow HDL seems to constitute

CYCLOFENIL

inal to eliminate the increased risk factor for de ment of heart attacks that lies in a low concentration L, we have used cyclofenil Cyclofenil is a synthetic teroid isomer of diethylstilboestrol It is a very weakly oestrogenic compound with anti-oestrogenic properties Its oestrogenic effect is 1/1000 of native oestrogen (8) Therefore it can be administered to men without oestrogenic side-effects It has been used with good results in the treatment of scleroderma (PSS) (2) as well as in gynaecological practice

PATIENTS

From a general preventive screening for risk factors un dertaken at the Department of Preventive Medicine Medical Clinic of Malmö General Hospital we selected 19 consecutive patients (aged 47-53 years) whose levels of APO AI placed them in the lowest five per cent and were thus below 90 These patients were screened with three separate analyses for APO-AI and their informed consent was obtained prior to participation in the study The 0-level was calculated and the patients were controlled bimonthly with the tests mentioned below The patients were instructed not to change their therapy diet exercise or daily living conditions during the study The initial dose of cyclofenil was 200 mg × 3

METHODS

Blood samples were drawn in the morning in the fasting state Serum was stored at +4 C until analysed within 48 hours Antiserum to human HDL isolated by ul racen trifugation was raised in rabbits and was found by crossed immunoelectrophoresis (7) to react only with APO AI

Serum cholesterol (15) and triglycerides (18) were de termined enzymatically Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) activity were determined with reagents from Boehringer Mann heim using a Vitatron Akes reaction rate analyser Gammaglutamyltransferase was determined with glu tamyl p-nitroanilide as substrate (14)

APO AI was determined by electroimmunoassay with frozen pooled human serum as standard as previously described (5) HDL cholesterol was determined after pre cipitation of low density lipoprotein (LDL) and very low density lipoprotein with dextran sulphate $MgCl_2$ (5)

Abbreviations HDL = high density lipoprotein LDL = low density lipoprotein APO AI = apolipoprotein AI ALAT = alanine aminotransferase ASAT = aspartate aminotransferase

Table I *Cl n cal d ti c the p t ents*

Pat no	Sex	Age (y)	APO AI (%) Initial	2 mo	4 mo	6 mo	Other prev ous d sea e	S de effects	Change after therapy
1	♂	48	78	90	95	95	None	None	
2	♂	47	83	110	95	115	Eczema	Sl ght revers ble r se in ALAT	Dim n hed after m
3	♂	48	86	90	105	100	Hypertens on obes ty	Th nks more clear N ne	
4	♂	52	117	125	115	115	None		
5	♂	53	105	120	110	110	Ang na pectoris	None	
6	♂	48	91	125	130	115	Ulcus duoden	Sl ght revers ble r e in ALAT	Dim n hed after 4 m
7	7♂	47	87	90	100		Ulcus duoden	Sl ght revers ble ep gastric pa n	Dim n shed after m
8	♂	48	88	105	120	105		Sl ght revers ble rise n ALAT	D m n hed after 4 mo
9	♂	47	77	80	85		Hypertens on urinary infec t on	Sl ght revers ble r se in ALAT after heavy al ohol intake	Dim e shed after 1 m
10	♂	48	85	100	100		Gastrit s	None	
11	♂	48	95	100			None	Sl ght revers ble rise in ALAT	D m n hed after 2 m
12	♂	48	85	105	115	95	Ulc s ventricul	None	D m n hed after 2 m non-cover
13	♂	48	90	110			Renal calcul	None	
14	♂	48	93	95			Lumbago	None	
15	♂	47	88	105			Gastrit s amputated l mb	Sl ght symptom of gastrit s	D m n she after 1 m
16	♂	47	90	105	135		None	None	
17	♂	48	88	110					
18	♂	48	85	80			Hypercholesterol aem a takes clof brate	Urt caria	F n shed after
19	♀	48	95				Eczema meno-pausal problems	Eczema d sappeared vag nal bleed ng	F n hed after

RESULTS

Table I gives the individual results and complica tions during the study

As ind cated in Table II APO AI levels showed a highly sign ficant rise of about 15% after two and four months of therapy ($p<0.000$ and 0.013 respec tively) There was also a s gn ficant rise in HDL cholesterol and probably correspond ng to th s a tendency to a rising cholesterol level LDL choles terol calcul ited as total cholesterol minus (HDL cholesterol plus triglycerides/2 28) d splayed a non sign ficant tendency to increase

C mpl cat ns

There was a tendency to slightly lower blood pres sure levels during treatment The transaminases were sl ghtly and transiently elevated in 6 patients It is well known from the PSS treatment stud es that a sl ght increase in ALAT is not qu te uncommon on rather high doses of cyclofenil (600 mg) it was reversed when the dose was redu ed to ... in t al level (300 mg) In gynaecol gical ... with daily doses of 200 mg such increa es ... uncommon As shown in Table II all 6 ... with a transam nase rise cont nued on a ... dose w thout further complications and ... the h gher APO AI level Vag nal b ... tient 19 seems to be postmenopausal as ... affected of term nat on of therapy

DISCUSSION

If one accepts the APO AI level or HDL cho... as an ind cator of the *HDL level it is ob ...* rise in HDL levels can be obtained by ... with cyclofen l Measured as APO AI t ... was about 15% Measured as HDL cho... increase was less wh ch suggests an alt... pos tion of the HDL A lower d se th... da ly could presumably be used as the ...

le II Var bles bef re c l (fter treat ent

	Time (mo)	No	0-level	After	? p (? ta led p obab l ty)
AI (?) (ref 5)	0-?	17	91 0	104 4	000
	0-4	10	9? 6	108 7	013
cholesterol (mmol/l)	0-?	17	0 80	0 86	014
	0-4	11	0 79	0 84	13?
e erol (mmol/l)	0-?	18	5 0	5 36	053
	0-4	1?	5 1	5 5	051
ycendes (mmol/l)	0-?	18	1 6	1 8	137
	0-4	1?	1 47	1 7	?31
T μkat/l)	0-?	18	0 35	0 54	149
	0-4	1?	0 36	0 6?	086
T (μkat/l)	0-?	18	0 36	0 75	090
	0-4	1?	0 39	1 03	115
D c BP (mmHg)	0-?	16	85 6	8? 8	070
	0-4	11	86 8	84 5	138
cholesterol (mmol/l)	0-?	17	3 51	3 71	?41
	0-4	11	3 66	3 89	?41

was ma nta ned even after the dose had been ed in the 6 pat ents Probably 300 mg daily w ll the des red result and avoid reversible side ls on the transam nases

th the short period of observation one can only nstrate that cyclofen l induces a h ghly s g ant rise n HDL levels Whether this increase is tent to confer a reduced risk of heart attacks is st on for long term prevent on studies

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REFERENCES

ubonak J J Anderson A J R mm A A & ing J F H gh dens ty l poprotein cholesterol and ronary artery occlus on Metabol sm ?8 735 1979

om Bulow B Bostrom H Herba G Persson Wol he m F & Öbe g K Cyclofen l n the ta ment of scleroderma. Z Rheumatol 39 230 80

adby G V H Valente A J & Walton K W rum h gh dens ty l poprote ns in peripheral vascular sea e Lancet ? 1271 1978

rew T E Kosch nsky T Hayes S B & Stein rg D A mechan sm by wh ch h gh-dens ty l po- o e ns may slow the atherogen c process Lancet 1315 1976

m el son B Ekman R Fex G Johansson B Kns ensson H N lsson Ehle P & Wadstein J anges in plasma h gh dens ty l poprote ns in ronic male alcoholics during and after abuse Scand ? n Lab Invest 38 113 1978

l tonal H gh dens ty l poprote n and atheroma ncet ? 1?91 1978

7 Ganrot P O Crossed mmunoelectrophores s Scand J Cl n Lab Invest (Suppl) 1?4 39 197?

8 Herbai G Treatment of progress ve system c scleros s w th a synthet c weak oestrogen cyclofen l Acta Med Scand 196 537 1974

9 Ish kawa T Fdge N Thelle D S Førde O H & M ller N E The Tromsø heart study Serum apol poprotein AI concentrat on n relat on to future coronary heart d sease Eur J Cl n Invest 8 179 1978

10 Johansson B G & Medhus A Increase in plasma α l poprote ns in chron c alcohol cs after acute abuse Acta Med Scand 195 ?73 1974

11 Laurell C B Compos t on and varia on of the gel electrophoret c fract ons of plasma cerebrosp nal flu d and urine Scand J Cl n Lab Invest (Suppl) 1?4 71 197?

1? Lehtonen A V ikari J & Ehnholm C The eff ct of exercise on h gh dens y (HDL) l poprote n apopro- te ns Acta Phys ol Scand 106 487 1979

13 Marx J L The HDL The good cholesterol car riers? Sc ence ?05 677 1979

14 Orlowski M & Meister A Isolat on of γ glutamyl transpept dase from hog k dney J B ol Chem ?40 338 1967

15 Roeschlau P Bernt E & Gruber W En zymat sche Best mmung des Gesamt-Cholesterins im Serum J Cl n Chem Cl n B ochem 12 2 6 1974

16 Ste n O Vanderhoek J & Ste n Y Cholesterol content and sterol synthes s in human sk n fibroblasts and rat aortic smooth muscle cells exposed to l popro- tein-depleted serum and h gh dens ty apol poprote n/ phosphol p d mixtures B och m B ophys Acta 431 347 1976

17 Ste nberg D The red scovery of h gh dens ty l po- prote n a negat ve risk factor in arterioscleros s Eur J Cl n Invest 8 107 1978

18 Wahlefeld A W Triglyceride determ nat on after enzymat c hydrolysis In Methods of enzymat c analys s (ed H V Bergmeyer) pp 1831 1838 Verlag Chem e We nhe m and Academic Press New York 1974

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Urinary Zinc Excretion during Treatment with Different Diuretics

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RACT Urinary zinc excretion was studied in domized trial in 9 patients during treatment bendroflumethiazide, chlorthalidone and hy lorothiazide and in another 9 patients during ent with bumetanide, furosemide and triam During treatment with the thiazides, the zinc tration rose by 30 % and the total amount of cretion increased by 60 % In contrast during ent with the loop-diuretics, urine zinc concen diminished and the total amount of zinc excre creased much less than during therapy with the les With respect to the importance of zinc as ential element in human metabolism and the ncy of diuretic treatment, the observed in d urinary losses of zinc deserve further atten-

ds u inary zinc excretion diuretics

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nportance of zinc in human metabolism has ed increasing attention since Prasad et al in itially described a zinc deficiency syndrome tans (11) Zinc deficiency may arise in several Severe nutritional deficiency leading to ism and hypogonad sm has been observed in 9 11) and Egypt (12) Mild nutritional defici in children causing reduced growth has been ed from the USA (18) Alcohol consumption to increased urinary zinc losses (14 15) and tc conten of the liver is very low in patients iver cirrhosis (17) In certain renal diseases n diabetes mellitus (2) and after surgical injury e urinary zinc excretion is raised Certain cdisorders and malabsorption especially acro itis enteropatica (6 7) lead to zinc defici In total parenteral nutrition zinc deficiency vided by Zn supplementation (3) Increased of zinc may also be iatrogenic Raised urinary x retion has been reported during treatment with penicillamine (1) During penicillamine therapy one patient developed a skin disorder resembling parakeratosis a well known zinc deficiency disorder in swine (10) Raised urinary zinc excretion has also been observed during treatment with chlorthalidone (19 20) and hydrochlorothiazide (8)

The aim of the present study was to investigate the urinary zinc excretion during treatment with six diuretic drugs bendroflumethiazide bumetanide chlorthalidone furosemide hydrochlorothiazide and triamterene

PATIENTS AND METHODS

Eighteen patients with untreated arterial hypertension 10 men and 8 women ranging in age from 33 to 75 years were included in the study Some clinical data on the patients are presented in Table I Their diastolic BP at the first visit to the hospital varied between 105 and 130 Patients 1 and 2 had enlargement of the heart S-creatinine values were normal in all patients GFR was measured in 10 of the patients The lowest value 71 ml/min was recorded in patient 3 The i v pyelogram was normal in all except patient 14 who had a left sided kidney stone None of the patients had proteinuria or signs of endocrine hyper tension

Patients 1-9 were treated with equipotential do es of bendroflumethiazide hydrochlorothiazide and chlorthali done for 2 weeks with each drug Patients 10-18 were treated with equipotential doses of triamterene furosemide and bumetanide for 2 weeks with each drug The patients were randomized as shown in Table II The treatment period was preceded by a one week control period 24 hour urine samples were collected throughout the control and treatment periods Specimens of the 24 hour collections were kept frozen until required for analysis Between each treatment period of 2 weeks there was one week without any treatment

Serum zinc was determined on the first and last day in every period Patients were told to avoid alcoholic beverages during the trial otherwise there were no dietary restrictions The zinc analyses were performed by atomic absorption (Varian Techtron Model 1100)

Student s paired t test was used in the statistical calculations

Table I *Clinical data on the patients subjected to the study*

Pat no	Age (y)	Sex	BP at 1st visit	Heart size (ml/m² BSA)	S-creatinine (mg/100 ml)
1	62	♂	190/130	670	1 2
2	47	♂	210/125	520	0 7
3	53	♀	185/115	320	0 6
4	74	♀	240/130	440	1 1
5	33	♂	195/120	380	1 0
6	56	♀	180/105	430	0 7
7	49	♀	180/115	400	0 6
8	75	♂	200/110	390	1 1
9	69	♂	190/110	400	1 2
10	62	♂	220/110	480	1 1
11	69	♂	190/110	400	1 2
12	53	♀	220/120	440	0 9
13	69	♂	180/110	350	1 0
14	56	♂	220/120	410	1 2
15	56	♀	190/115	360	0 9
16	43	♂	180/130	380	1 1
17	69	♀	220/110	330	1 0
18	67	♂	220/120	400	0 9

RESULTS

The urinary zinc excretion in patients 1–9 before and during treatment with bendroflumethiazide chlorthalidone and hydrochlorothiazide is presented in Table III The pretreatment values are mean values of 7 24 hour collections and the values for treatment periods are mean values of 14 24 hour collections A highly significant increase in urinary zinc excretion of about 300 µg/day was observed during treatment with all three drugs The zinc concentration in the urine also increased but not to the same extent During treatment with bendroflumethiazide and hydrochlorothiazide the concentration increased by 1 6 mmol/l ($p<0\,01$) The increase in concentration during treatment with chlorthalidone was 1 8 mmol/l (p 0 001)

Table IV presents the urinary zinc excretion before and during treatment with bumetanide furosemide and triamterene Significant increases in zinc excretion of about 100 µg were obtained during treatment with all three drugs This increase was smaller than that during treatment with the thiazides and no increase in zinc concentration was seen On the contrary lower though not significantly lower zinc concentrations were found during treatment with furosemide and bumetanide

Serum zinc was within the normal range in all patients before treatment and in all (who successively developed hypozincemia) treatment with the different diuretics The values of serum zinc after treatment with different diuretics did not differ significantly from each other or from the mean pretreatment value

DISCUSSION

None of the patients in the present study were alcoholics or had diabetes proteinuria or any other known reason for increased or decreased urinary zinc excretion The 24 hour zinc excretion in the 18 untreated hypertensive patients agrees fairly well with earlier published values of untreated hypertensive patients and of normotensive subjects (4) Serum zinc values were also within the normal range in all untreated patients

During treatment with equipotential doses of bendroflumethiazide chlorthalidone and hydrochlorothiazide a highly significant increase in zinc excretion was observed This increase was about the same for all three diuretics bendroflumethiazide and hydrochlorothiazide, chlorthalidone 65% (Table V) The increased amount of zinc excreted during treatment was partly an effect of raised zinc concentration in urine and (31–35% Table V) an effect of increased urine volumes About the same increase in urine

Table II *Randomization of the treatment*

Pat no			
1 2 3	Bendroflumethiazide	Hydrochlorothiazide	Chlorthalidone
4 5 6	Hydrochlorothiazide	Chlorthalidone	Bendroflumethiazide
7 8 9	Chlorthalidone	Bendroflumethiazide	Hydrochlorothiazide
10 11 12	Triamterene	Furosemide	Bumetanide
13 14 15	Furosemide	Bumetanide	Triamterene
16 17 18	Bumetanide	Triamterene	Furosemide

III *Mean urinary zinc excretion before and during treatment with bendroflumethiazide chlor... ne and hydrochlorothiazide*

During 7 days without medication (mg/24 h)	(mmol/l)	During 14 days treatment with Bendroflumethiazide (mg/24 h)	(mmol/l)	Hydrochlorothiazide (mg/24 h)	(mmol/l)	Chlorthalidone (mg/24 h)	(mmol/l)
0 71	6 5	1 17	10 6	0 73	6 5	0 89	7 5
0 76	12 5	1 38	13 1	1 47	12 3	1 81	14 5
0 76	2 6	0 32	3 6	0 34	5 4	0 30	4 0
0 18	1 7	0 53	4 1	0 31	3 5	0 54	5 9
0 40	3 5	0 47	2 3	0 95	5 7	0 59	3 7
0 57	5 7	0 75	7 5	0 67	7 0	0 66	7 3
0 51	5 2	0 80	6 8	0 81	6 9	0 84	7 1
0 46	3 4	0 83	6 0	0 93	6 8	0 81	5 8
0 48	5 5	0 70	7 3	0 72	7 0	0 65	7 6
S D 0 48±0 19	5 2±3 2	0 77±0 33	6 8±3 4	0 77±0 35	6 8±2 4	0 79±0 42	7 0±3 1

on during treatment with chlorthalidone was ed in an earlier study (20) and this increase ed after half a year s treatment (21) Pak et al o investigated urinary zinc excretion in 8 s during treatment with hydrochlorothiazide tained a zinc augmentation of the same order mitude which persisted after one month of In the present study no differences in zinc increment were observed between pa who started with a particular drug and those ere treated with the same drug at the end of dy

ontrast to the thiazides the loop-diuretics a diminished concentration of zinc in urine treatment (Table V) Nevertheless the total of zinc excreted increased somewhat de on the large urine volumes produced

Thus the renal handling of zinc is influenced differently by thiazides and loop-diuretics and in an opposite direction compared to calcium Steel (13) found that the zinc concentration in urine diminished considerably during the first two hours after i v injection of furosemide and etacrynic acid but that the total amount of zinc excreted increased After isotonic saline loading he also noticed an increased zinc excretion and concluded that zinc excretion bears at least some relationship to urine flow During treatment with triamterene the zinc concentration in urine did not change in the present study but the urine volumes and thus the total excretion of zinc increased somewhat

Thus during diuretic treatment especially with thiazides the amount of zinc lost in the urine is raised and this effect persists during long term

IV *Mean urinary zinc excretion before and during treatment with bumetanide furosemide and ... rene*

During 7 days without medication (mg/24 h)	(mmol/l)	During 14 days treatment with Bumetanide (mg/24 h)	(mmol/l)	Furosemide (mg/24 h)	(mmol/l)	Triamterene (mg/24 h)	(mmol/l)
0 39	6 1	0 67	4 9	0 36	4 4	0 48	5 8
0 50	5 5	0 52	4 4	0 53	4 5	0 65	7 5
0 36	5 7	0 40	4 8	0 37	3 6	0 38	5 4
0 35	5 4	0 37	4 7	0 38	5 1	0 39	6 7
0 76	10 2	0 80	12 6	0 95	12 3	0 79	7 0
0 58	6 2	0 75	6 8	0 90	9 9	0 66	7 3
0 73	6 1	0 71	4 8	0 64	4 3	0 75	5 2
0 47	7 9	0 49	4 2	0 49	4 8	0 47	5 0
0 33	4 3	0 36	3 5	0 36	3 5	0 64	7 7
S D 0 49±0 17	6 4±1 7	0 56±0 17	5 6±2 8	0 55±0 23	5 8±3 4	0 58+0 15	6 4+1 1

Table V *Change (%) in urinary zinc excretion between values observed without and with treatment with six diuretics*

	Amount	Concentration
Bendroflumethiazide	60	31
Chlorthalidone	65	35
Hydrochlorothiazide	60	31
Bumetanide	*14*	*−14*
Furosemide	12	−13
Triamterene	18	0

treatment In spite of this fact the serum zinc concentration is normal or even slightly raised during diuretic therapy but *if this is dependent on increased* zinc absorption or tissue zinc depletion remains to be clarified It is also unclear if the increased urinary losses of zinc will lead to a zinc deficiency of clinical significance *However* since diuretic treatment is very common and zinc has been recognized as an essential element for human *health the diuretic–zinc problem calls for further* attention

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REFERENCES

1 *Boström H & Wester P O On the excretion of* trace elements in two penicillamine treated cases of cystinuria Acta Med Scand 181 475 1967

2 Constam G R Leemann W & Almasy F Über die Zinkausscheidung im Harn beim Diabetiker Schweiz Med Wochenschr 88 1103 1958

3 Jacobsson S & Wester P O Balance study of twenty trace elements during total parenteral nutrition in man Br J Nutr 37 107 1977

4 Kahn A M Helwig H L Redecker A G & Reynolds R B Urine and serum abnormalities in disease of the liver Am J Clin Pathol 44 426 1965

5 Lindeman R D Bottomley R G Cornelison Jr R L & Jacobs L A Influence of acute tissue injury on zinc metabolism in man J Lab Clin Med 79 452 1972

6 Michaelson G Acrodermatitis en[illegible] ference on Zinc in Medicine Lund 197[illegible]

7 Moynahan E J Acrodermatitis en[illegible] thal inherited human zinc deficiency d[illegible] 2 399 1974

8 Pak C Y C Ruskin B & Diller E [illegible] of renal excretion of zinc by hydro[illegible] Clin Chim Acta 39 511 1972

9 Prasad A S Metabolism of zinc and [illegible] in human subjects In Zinc metabolism [illegible] Prasad) Thomas Springfield 1966

10 — Zn deficiency in man considerations [illegible] anemia and other medical disorders Paper [illegible] *17th annual session of the American Colle[illegible]* tion In The American College of Nu[illegible] *lecture Montreal May 1976*

11 Prasad A S Miale Jr A Farid Z Sa[illegible] *H & Schulert A R Zinc metabolism [illegible]* with the syndrome of iron deficiency [illegible] hepatosplenomegalia dwarfism and hypo[illegible] Lab Clin Med 61 537 1963

12 *Sandstead H H Prasad A S Sch[illegible]* Farid Z Miale Jr A Bassily S & Da[illegible] Human zinc deficiency endocrine manifest[illegible] response to treatment Am J Clin Nutr 20 [illegible]

13 Steele T H *Dissociation of zinc excr[illegible]* *other cations in man J Lab Clin Med 81 [illegible]*

14 Sullivan J F Zinc deficiency and chron[illegible] ism Clinical application on zinc metab[illegible] *land Ohio Oct 1971*

15 Sullivan J F & Heaney R P *Zinc [illegible]* alcoholic liver disease Am J Clin N[illegible]

16 Underwood E J Trace element in hum[illegible] *mal nutrition p 208 Academic Press* [illegible] 1971

17 Vallee B L Wacker B L C Bartholom[illegible] & Hoch F L Zinc metabolism in hepa[illegible] *tion Ann Intern Med 50 1077 1959*

18 Walravens P A Zinc nutrition and [illegible] pediatrics Paper read at the 17th annual se[illegible] American College of Nutrition Montreal [illegible]

19 Wester P O Spårelement vid hyperten[illegible] under tiazidbehandling (abstract) Paper [illegible] meeting of the Swedish Medical Society [illegible] 1970

20 — Trace elements in serum and urine [illegible] tensive patients before and during treat[illegible] chlorthalidone Acta Med Scand 19[illegible]

21 — Trace elements in serum and urine [illegible] sive patients treated for six months [illegible] thalidone Acta Med Scand 19[illegible]

Electrocardiographic Diagnosis of Ventricular Septal Infarction

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TRACT To find electrocardiographic criteria ... entricular septal infarction two series of ECGs ... studied all without fascicular/bundle branch ... and complete heart block One series consisted ... ECGs recorded at thallium 201 scintigraphy in ... tients 2-3 weeks after an acute myocardial in... tion (AMI) In this series the 14 patients with a ... t in the septal wall of the left anterior oblique ... were compared with the 35 without The other ... consisted of the last premortal ECGs in 20 AMI ... nts with and in seven without a septal involve... of the infarct at autopsy The best criterion ... earlier literature was absence of a q wave in ... V_6 showing a sensitivity of 53 % in the combined ... graphy and autopsy series The predictive val... a positive test was 75 % The very first QRS ... in the frontal plane tended to discriminate ... r than absence of a q in lead V_6 With a similar ... ictive value 71 % the sensitivity of a deviating ... r (+120° to −60 and −120 to −180) was 65 % ... e combined scintigraphy and autopsy groups ... of the patients with a deviating vector showed ... n admission The clinical importance of an early ... osis of septal involvement in AMI remains to be ... d

...words ventricular septal infarction electrocardio... myocard al scintigraphy

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... 12-lead electrocardiogram (ECG) does not in... e the precise location of a myocardial infarct in ... ft ventricle (8) but it is reliable in distinguish... nfarcts involving the anterior from those involv... he inferior/posterior wall (5) which has a prog... c implication (2) From the prognostic point of ... the ventricular septum might well be the most ... rtant wall as it influences the pump function of ... ventricles and carries the main parts of the ... ventricular conduction system Based on au... y studies septal infarcts are however stated not to produce any specific ECG pattern (5) Today septal infarcts can be detected in vivo by thallium 201 scintigraphy and one can re assess the problem of diagnosing them on ECG

The aim of this study was to compare the ECGs in patients with and without septal involvement of a myocardial infarct according to thallium 201 imaging in one series and to autopsy in another Three ECG patterns were suggested many years ago as indicating septal involvement qrs complexes in leads V_1 (4) QS in V_{1-4} (6) and disappearance of the normal q wave (3) As the ventricular activation normally starts in the septum it was also considered worthwhile to study the frontal vector of the first QRS deflection

PATIENTS AND METHODS

Thallium 201 scintigraphy series

Fifty five non-consecutive patients with acute myocardial infarction (AMI) were studied before discharge from hospital usually during the second or third week after the infarction The main selection mechanism was that a thallium 201 dose was available during the last days before discharge Fifty-one males and four females were included aged 37-79 years (mean 58 3) Twelve of them had a history of previous AMI The current AMI was diagnosed on the basis of history serial ECG and serial serum enzymes (CK ASAT ALAT LDH) The ASAT maximum was 0 8-14 3 median 2 9 μkat/l (upper normal limit 0 7)

In 50 of the 55 patients the dose 75 MBq thallium 201 was injected i v during exercise on a bicycle ergometer in the other five this was done at rest Imaging was started 10 min after the injection using a Nuclear Chicago Pho Gamma camera with high resolution collimation Polaroid scintiphotographs 400 000 counts were obtained in the anterior 45 left anterior oblique (LAO) and left lateral

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Abbreviations ECG = electrocardiogram AMI = acute myocardial infarction CCU = coronary care unit LAO = left anterior oblique

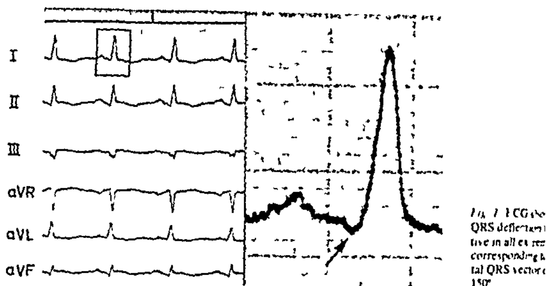


Fig 1 ECG ... QRS deflection ... tive in all ex... corresponding ... tal QRS vector ... 150°

projections The imaging was repeated 2–4 hours later if a defect was detected in any projection at the immediate imaging These second images together with those after injection at rest were used for the correlation to various patterns of a 12 lead ECG taken at rest immediately before the injection procedure All images were studied for defects in the septal wall in the LAO projection by two observers working independently The defects were classed as definite or probable

Autopsy series

Thirty seven consecutive autopsied AMI patients were collected from the files of the coronary care unit (CCU) and the post CCU ward Twenty four were males and 13 females aged 47–85 years (mean 68 6) Sixteen of them had a history of previous AMI The ASAT maximum of the current AMI was 1 2–12 6 median 6 4 μkat/l The interval between onset of AMI symptoms and death was 1–71 days (mean 7 3) The most common causes of death were shock 16 rupture 5 heart failure 3 and unexpected ventricular fibrillation/asystole 5 A routine autopsy was performed The last premortal ECG 0–13 days (mean 1 9) before death without complete heart block and fascicular/bundle branch block was used for correlative studies

The ECGs from the scintigraphy and autopsy series were studied for fascicular block bundle branch block complete heart block and artificial pacing If none of these was present qrs configuration in leads V_1 or V_2 or QS in V_3 or V_4 was noted as was the absence of q in V_6 The frontal vector angle was also determined based on the first QRS deflection in the six extremity leads (Fig 1) and classified in steps of 30 degrees (−165 −135 ... +135 or +165° e g a vector of −165 implies between −180° and −150°) For comparison the initial (0 04 sec) vector was also estimated in steps of 30 degrees

The ECGs were interpreted by two observers working independently one of them without any knowledge of the scintigraphy or outcome of the autopsy In the event of different interpretations of ECGs or scintigrams a third observer s opinion was decisive

The exact treatment was used instead of t... fourfold tables (1)

RESULTS

Thallium 201 scintigraphy series

At the time of scintigraphy no patient ha... heart block but six had fascicular or bun... block Only one of these six patients ... septal image defect

Of the remaining 49 patients 10 showe... septal image defect and four a probable ... qrs configuration in V_1 or V_2 nor a QS co... in V_3 or V_4 was significantly more comm... patients with than without definite septa... but this was the case for absence of a q wa... V_6 (Table I) The sensitivity for absence ... was however rather low 50%

In three patients all without a septal ... fect the first QRS vector could not be d... unequivocally probably because the first ... was so small that it was not discernible ... tremity leads The distribution of the freq... in the remaining 46 cases is presented in F... patients without septal image defects ar... nantly at −105 −75 +135 and +165 ... other vectors as deviant their incidence ... nificantly higher in patients with than w... nite septal image defects i e 8/10 agai... sensitivity tends to be higher than for abse... in V_6 80% against 50% and the predictive ... a positive test is similar 53% and 56% re... ly Ten of the 16 patients with a deviant

| ECG cl nges (%) n tl e tl all s nt gr pl ser es a d tl e a ops se es

	Thall um sc n gram series			Autopsy series			
	Def n e sep al defect (n 10	Probable sep al defect (n 4)	No sep al defect (n 35)	Large sep al nfarct (n 7)	Small septal nfarct (n 7)	Impre e septal nfarct (n 6)	No ep a nfarct (n 7
\	30	0	6	14	0	33	29
\	40	5	11	14	0	0	14
m \	50	25	11*	86	43	50	9
n f rs QRS ecto			n 3				
13 o 45 105°)	80	50		86	43	50	9

n f an d fference (p 0 05)

d th s on the f rst ECG and n the rema n ng de eloped during the f rst 15 days n hosp tal ev ant vector was not assoc ated s gn f cantly often w h anterior or nferior/posterior s te of farct acco d ng to ECG although anterior n were o er represented n the group with sep-lO defects ($p<0.05$)

f rst QRS vector was not correlated to the frontal QRS vector (r 0 10) Th s first QRS r was also compared to the so called n t al sec) QRS vector in the frontal plane in 43 s They corresponded in only four pat ents sually d ffered 30° 90°

tal nfarcts are stated to be detectable also n edial wall n the anterior sc nt graph c projec but the f rst QRS vector of pat ents w th a t n the upper part of that wall was d stributed he rest of the pat ents The same holds true fects n the lower part of the medial wall in the o project on Thus only the LAO project on mina ed pat ents w th d fferent vectors

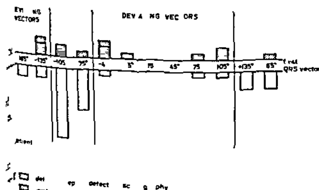
two observers d ffered regard ng a septal LAO defect n f e of the 55 s nt grams Th re va no d sagreement regard ng qrs n V QS in V_3 q in V_6 or the f rst QRS vector

T o of these 49 pat ents w thout complete heart block or fasc cular/bundle branch blo k at sc nt graphy had a temporary complete heart block for some t me during the hosp tal stay and two showed temporary bundle branch blo k One of these four pat ents had a septal mage defect

A t psy ser es

A septal nvolvement of the nfa ct def n te or probable was much more common in the decea ed accord ng to autopsy (73%) than n the surv vors accord ng to the LAO project on n the thall um 01 scint gram (27%) ($p<0.05$)

In 10 of the 37 autops ed pat ents all ECG showed complete heart block or fascicular/bundle branch block and could not be evaluated w h e gard to the various QRS patterns s ud ed (3 of 10 with large 3 of 10 th small 1 of 7 w h mpre se and 3 of 10 w thout septal involvement) Absen e o



F g 2 D s ribu on of the f rst QRS ec o n pat ents w th septal mage defect n the LAO project on (upper part) and w thou such defect (lower part)

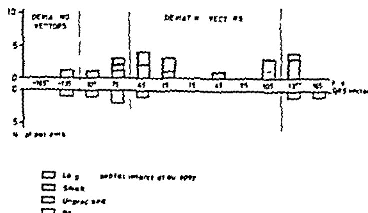


Fig 3 Distribution of the f... in patients with septal infa... (upper part) and without septal... (lower part)

q in lead V_6 was more common in patients with large than with no septal involvement (p=0 05) (Table I)

The first QRS vector could be determined in all 27 patients without complete heart block or fascicular/bundle branch block (Fig 3) Patients with large or no septal involvement at autopsy are distributed similarly to those with definite or no septal image defect at scintigraphy Deviating vectors i e others than −105° −75 +135° and +165° were found in six of the seven patients with large septal infarcts and in only two of the seven without septal involvement (p=0 05) The groups with small and imprecise septal infarcts were in between (Table I)

Eight of the 27 patients without fascicular/bundle branch block or complete heart block in all ECGs had a temporary complete heart block and they were rather evenly distributed in the four subgroups Two of these seven patients and six others showed temporary bundle branch block and there was no dominance for any subgroup in this respect

The two observers did not differ regarding the occurrence of qrs in V_{1-2} QS in V_{2-4} or q in V_6 but in three cases the vector differed one step (30°)

DISCUSSION

A septal involvement of the infarct was found more frequently in the autopsy series (73%) than in the scintigraphy series (27%) This difference may have several explanations The infarcts of the survivors were smaller as measured by S-ASAT (p<0 05) and hence a detectable septal involvement is less likely Furthermore a small septal infarct may pass undiagnosed more easily at scintigraphy than at autopsy In this series the scintigraphic diagnosis of a septal infarct was made only in the LAO projection and excluding the an... ection may have given some false nega... However as defects in the anterior co... LAO position did not discriminate ... different first QRS vectors the an... appears to reveal only a small fraction of ... infarcts or infarcts so located e g h... are not reflected by the very first part of the...

According to experimental studies ... by Scher (7) the very first QRS acti... superiorly rightward and anteriorly Th... sponds well to first QRS vector in the ... of −105° which was found in 14 of the ... without a demonstrable septal infarct (Fig 3) Eight of the 39 had however a first QRS of +135° or +165° and that was not ex... different heart position as measured by the QRS axis Nor did they show with one ex... defect high in the medial wall in the an... tion

The interpreter variation in determ... QRS vector was small only 4% of the ... fered between two independent observers ... only one step (30°) The sensitivity of a ... vector is acceptable (65% for all infarct ... combined scintigraphy and autopsy series ... predictive value of a positive test (71% ... combined series) The predictive value ... for absence of q in V_6 75% but the ... tends to be less 53%

It could be discussed if a vector in the ... −120° to −180° should be considered as ... not In this sector there were altogether ... tients with signs of septal infarct and ... (Figs 2+3) Considering those vectors ... reduces the sensitivity to 53% the ... absence of q in V_6 and increases the ...

e to 82% which should be compared to 75% bsence of q in V_6

seems reasonable that the first QRS vector d show a better sensitivity than qrs in V_1 QS $_{3-4}$ and absence of q in V_6. These patterns are confined to the first csec of QRS when the ncular activation starts in the septum. Analog y this first QRS vector differs from the so-called d one (0.04 sec).

e clinical importance of early diagnosis of a al involvement remains to be settled although a nt echocardiographic study of anterior infarc showed septal involvement to be correlated to development of heart failure and bundle branch (9). In the present retrospective series the t on pump function of a septal involvement in cannot be studied as all patients were treated hylactically with rather high doses of diuretics.

e incidence of complete heart block did not r between patients with and without septal in ment in the present combined scintigraphy autopsy series (16% and 28% respectively). lle branch block however was significantly common in patients with septal involvement against 6%, $p<0.05$).

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REFERENCES

1. Fisher R A. Statistical methods for research workers. 13th ed., p 96. Oliver and Boyd, Edinburgh 19 5.
2. Goldberg R J, Kennedy H L, Szklo M & Tonascia J. Prognosis of anterior myocardial infarction revisited. Am J Cardiol 43: 370, 1979.
3. Levy L & Hyman A L. Difficulties in the electrocardiographic diagnosis of myocardial infarction. Am Heart J 39: 243, 1950.
4. Myers G B, Klein H A & Hiratzka T. Correlation of electrocardiographic and pathologic findings in infarction of the interventricular septum and right ventricle. Am Heart J 37: 720, 1949.
5. Roberts W C & Gardin J M. Location of myocardial infarcts. A confusion of terms and definitions. Am J Cardiol 42: 868, 1979.
6. Rodrigues M I, Anselmi A & Sodi Pallares D. The electrocardiographic diagnosis of septal infarctions. Am Heart J 45: 525, 1953.
7. Scher A M. Excitation of the heart. A progress report. In: Advances in electrocardiography (ed. R C Schlant & J W Hurst), p 70. Grune & Stratton, New York 1972.
8. Sullivan W, Vlodarer Z, Tuna N, Long L & Edwards J E. Correlation of electrocardiographies and pathologic findings in heal d myocardial infarction. Am J Cardiol 42: 724, 1978.
9. Wiener I, Meller J, Packer M, Herman M V & Teichholz L E. Prognostic value of echocardiographic evaluation of septal function in acute anteroseptal myocardial infarction. Am Heart J 97: 726, 1979.

Thallium-201 Scintigraphy after Acute Myocardial Infarction

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RACT Fifty five patients with acute myocar farction were examined with thallium 201 scin hy before discharge from hospital Fifty one d significant scintigraphic defects The number ormal Q waves in a 12 lead ECG but not the al ASAT value for each patient were corre o the total estimated image defect Mortality the follow up period of 14–28 months was not l to the estimated total image defect but the rly deaths occurred among patients with the lilated left ventricles

ords thallium 201 scintigraphy acute myocardial ion

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emaining amount of viable left ventricular rdium and its functional state are reasonably tant prognostic factors following an acute rdial infarction (AMI) Serum enzyme maxi ring the acute phase give a rough estimate of e of the current infarct Cold spot myocar intigraphy can give information about the nyocardial loss in current and previous AMI ent ischaemia of the remaining myocardium evaluated at the same time by injecting thal-01 (^{201}Tl) during exercise and imaging im lely and after 4 hours (6 8) The scintigram rovides some information about left ventricu ilation

l scintigraphy has been used following AMI recent multicenter study of 145 AMI patients the hospital stay (7) concluded that the d complements the electrocardiographic identification of the infarct The present concerns another aspect what does ^{201}Tl rdial imaging add to the information that can be obtained about the remaining amount of viable myocardium and its functional state from history ECG serum enzyme maxima and chest X ray ?

PATIENTS AND METHODS

Fifty five consecutive AMI patients 51 males 4 females aged 37–79 years (mean 58 3) were studied before discharge from hospital usually during the second or third week after an infarction The main selection mechanism was that a ^{201}Tl dose was available during the last days before discharge Twelve patients had a history of previous AMI The current AMI was diagnosed on the basis of history serial ECG and serial serum enzymes (CK ASAT ALAT LDH) The ASAT maximum was 0 8–14 3 median 2 9 µkat/l (upper normal limit 0 7) Twenty of the infarcts were anterior (ANT) 27 diaphragmal and four lateral according to serial ECG four were not localizable

A chest X ray and ^{201}Tl scintigraphy with injection during exercise were performed before discharge The he t X ray was taken in the standing position and the heart volume was calculated (4) The upper normal limit used were 500 ml/m² BSA for males and 450 ml/m² BSA for females Radiological heart volume is not available in four patients

For the scintigraphic examination 75 MBq ^{201}Tl was injected i v during exercise in the sitting position on a bicycle ergometer in 50 of the 55 patients The injection was given about 2 min before termination of the exercise on a load of 40–160 W (median 60) Most bicycle tests were discontinued before the patients had developed any symptoms Because of heart failure the remaining five patients were injected at rest in the standing position to reduce splanchnic blood flow and thereby uptake by the liver

Imaging was started 10 min after the ^{201}Tl injection Images were obtained in the ANT 45 left anterior oblique (LAO) and left lateral (LL) projections Imaging was re

Abbreviations ^{201}Tl = thallium 201 AMI = acute myocardial infarction ECG = electrocardiogram electrocardiographic ANT = anterior LAO = left anterior oblique LL = left lateral

Fig 1 Estimated total image defect (score 0–30) for each patient immediately after ^{201}Tl injection in relation to the number of abnormal Q waves (0–10) in the ECG recorded at scintigraphy

peated 2–4 hours later in 42 patients using the projections that visualized best the image defects

The gamma camera was a Nuclear Chicago Pho Gamma HP Converging collimation was used An energy window of 35% was set symmetrically over the 69–80 keV X ray spectrum In each projection 400 000 counts were collected on Polaroid scintiphotograms and in a Nuclear Data Med II computer system Linear interpolation from the basic 64×64 matrix into a 256×256 matrix was performed on the computer images

All images were interpreted by three observers who were not aware of the clinical details A significant defect was considered present if a region of decreased activity demarcated in both basal and apical directions was observed The ANT and 45 LAO images were divided into three and the LL image into four segments The defects were graded from 1 to 3 for each segment depending on the degree and extension of the decrease in activity The theoretical maximum score was 30 Images obtained about 2–4 hours later were interpreted in the same way and these later images were used for all correlative studies except for those 13 patients in whom only the initial imaging was performed The degree of the left ventricular dilatation in the scintigram was estimated in a scale from 0 to 2

The 12 lead ECG recorded at the scintigraphic examination was studied for abnormal Q waves (≥0 04 sec) in leads I II III a VL AVF V_{1-6} by three observers

The patients were followed with regard to survival for 14–28 months (mean 20 6)

RESULTS

Fifty one of the 55 patients had significant ^{201}Tl scintigraphic defects at the imaging immediately after exercise including 39 (91%) of the 4[illegible] without prior AMI The defect score [illegible] (mean 6 0) The 38 patients who showed [illegible] the first scintigraphy and were re exam[illegible] hours later had a defect score of 1–15 (me[illegible] the first imaging and 1–15 (mean 3 6) at th[illegible] ($p>0$ 05) Sixteen patients showed redistri[illegible]

Abnormal Q waves in the 12 lead ECG [illegible] just before the scintigraphy were found in [illegible] 55 patients A significant correlation [illegible] $p<0$ 01) was found when the number of abn[illegible] waves in leads I II III aVL AVF V_{1-6} [illegible] patient was related to the image defect sc[illegible] 1) Patients with a history of previous A[illegible] scattered among those without any kno[illegible] event

The image defect score did not correlate [illegible] ASAT maximum even when the 18 patient[illegible] history of previous AMI or with a falsely to[illegible] too low ASAT maximum were excluded [illegible] too high ASAT maximum was considered [illegible] when the increase in ALAT was more tha[illegible] the increase in ASAT (acute liver damage) [illegible] maximum was considered falsely too low [illegible] patient because of the long interval (72 ho[illegible] tween onset of symptoms and admission to [illegible] tal

The frequency of abnormal Q waves in [illegible] with image defects was related lead by le[illegible] segment by segment to the average frequenc[illegible] series No abnormal Q wave in lead I or sig[illegible] image defect in the posterior segment of [illegible] projection were found When compared w[illegible] average distribution a marked overreprese[illegible] of abnormal Q waves was found in lead aVL [illegible] anterolateral segment of the ANT project[illegible] lead V_2 in the anterior and in lead aVF in [illegible] ferior segment of the LL projection

At the time of follow up five patients ha[illegible] They did not have a significantly higher [illegible] score than the survivors

The relation between the dilatation of t[illegible] ventricle estimated from the scintigram a[illegible] radiological heart volume is shown in Table [illegible] the largest heart volumes were associated [illegible] marked scintigraphic dilatation of the left ve[illegible] but high-degree dilatation was also com[illegible] hearts with normal radiological volumes Th[illegible] deaths within three months after scintigra[illegible] curred among the five patients with the larges[illegible] tigraphic and radiological dilatation the [illegible]

Table I. Estimated degree of left ventricular dilatation on scintigrams and radiological heart volume

Degree of scintigraphic left ventricular dilatation	Radiological heart volume (ml/m² BSA) Normal	Moderate increase (<100)	Marked increase (>100)
None	18	6	0
Moderate	10	6	0
Marked	3	3	5

(9-18 months later) were scattered among the groups presented in Table I.

DISCUSSION

All patients without evidence of prior AMI in a multicenter study (7) 81% had 201 Tl image defects during hospitalization for AMI. In the present series the corresponding figure was 91%. A similar incidence of new abnormal Q waves (64 and 68%, respectively) speaks in favour of a similar average infarct size in the two series. The difference in the frequency of positive 201 Tl scintigrams (81 against ...) may be due to differences in the criteria for a significant image defect. An infarct must have a certain size to be detectable by 201 Tl scintigraphy according to both experimental and clinical experience (5). The location of the infarct may also be of importance, e.g. in this series no defect in the posterior wall fulfilled the criteria of a significant defect.

The total number of abnormal Q waves correlates well to the image defect score, but the scatter is large. Abnormal Q waves after AMI may disappear with time (?) and the criterion of a Q wave ... sec does not detect more than 61% of infarcts diagnosed at autopsy (3). How ... Tl scintigraphy correlates with autopsy in a large clinical ... remains to be seen.

The exercise test was performed with caution ... was usually terminated before symptoms or ... appeared; neither the ECG nor the scintigrams are fully conclusive with regard to the presence of ischaemia. Redistribution on 201 Tl scintigrams after exercise seem however to have a ... sensitivity for myocardial infarcts than ... after injection at rest (1).

In conclusion, this series suggests that 1) 201 Tl scintigraphy 2-3 weeks after an AMI demonstrates defects in most cases reflecting the current infarct and probably also undiagnosed prior infarcts. Mortality during the following 14-28 months is however not related to the estimated total image defect. Studies of the patients' functional state after the hospital phase in relation to the remaining amount of viable myocardium are needed. 2) 201 Tl scintigrams performed after injection during exercise give some information about ischaemia in the remaining viable myocardium. Image defects that diminished or disappeared in 2-4 hours were seen in about one third of the patients. 3) Tl scintigrams offer a possibility of a rough estimation of left ventricular dilatation which seems to be related to short term survival after the hospital phase.

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REFERENCES

1. Blood D K, McCarthy D M, Sciacca R R & Cannon P J: Comparison of single-dose and double-dose thallium-201 myocardial perfusion scintigraphy for the detection of coronary artery disease and prior myocardial infarction. Circulation 58: 777, 1978.
2. Forssell G: Värdet av några avledningars EKG för diagnostik av akut hjärtinfarkt, p. 49. Thesis, Stockholm 1977.
3. Horan L G, Flowers N C & Johnson J C: Significance of the diagnostic Q wave of myocardial infarction. Circulation 43: 428, 1971.
4. Jonsell S: A method for the determination of the heart size by teleroentgenography (a heart volume index). Acta Radiol 20: 325, 1939.
5. Mueller T M, Marcus M L, Ehrhardt J C, Chaudhuri T & Abboud F M: Limitations of thallium-201 myocardial perfusion scintigrams. Circulation 54: 640, 1976.
6. Pohost G M, Zir L M, Moore R H, McKusick K A, Guiney T E & Beller G A: Differentiation of transiently ischaemic from infarcted myocardium by serial imaging after a single dose of thallium-201. Circulation 55: 294, 1977.
7. Ritchie J L, Zaret B L, Strauss H W, Pitt B, Berman D S, Schelbert H R, Ashburn W L, Berger H J & Hamilton G W: Myocardial imaging with thallium-201: A multicenter study in patients with angina pectoris or acute myocardial infarction. Am J Cardiol 42: 345, 1978.
8. Strauss H W, Harrison K, Langan J K, Lebowitz E & Pitt B: Thallium-201 for myocardial imaging. Relation of thallium-201 to regional myocardial perfusion. Circulation 51: 641, 1975.

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Effect of Metoprolol on QT_c Intervals after Acute Myocardial Infarction

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[ABST]RACT The effect of metoprolol on corrected [QT i]nterval (QT_c) was studied retrospectively in 111 [survi]vors of AMI below 70 years of age Prior to [disch]arge the patients were stratified by age in[farcti]on size and ventricular arrhythmias and ran[domiz]ed Metoprolol, 100 mg b i d or placebo were [given] double-blindly to 59 and 52 patients, respec[tively] QT_c intervals were measured four times prior [to ran]domization and three times during the follow [up ye]ar The highest QT_c mean was registered on the [secon]d day in the CCU QT intervals subsequently [decre]ased significantly in both groups between dis[charg]e and the three month control ($p<0.001$) [Patien]ts on metoprolol had significantly shorter QT_c [inter]vals during the follow up year than those [on p]lacebo (0.394 ± 0.028 vs 0.406 ± 0.034 sec, [p<0.0]01) The QT_c shortening effect of β receptor [block]ade was most marked in patients with pro[longe]d QT_c intervals at discharge Patients who died [sudde]nly had prolonged QT_c intervals prior to dis[charg]e In this group the proposed beneficial effect of [β rece]ptor blockade on QT_c interval cannot be [evalua]ted as most of these patients had died before [the fir]st control

[Key w]ords QT interval acute myocardial infarction [β rece]ptor blockade

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[Patien]ts with previous myocardial infarction (MI) [and c]onstantly prolonged corrected QT intervals (>440 msec) have been found to run a higher [risk of] dying suddenly (21) Furthermore survivors [of out]-of hospital ventricular fibrillation (VF) have [been f]ound to have longer QT_c intervals than other [ambul]atory post MI patients (10) We found that [patien]ts with AMI who developed ventricular [tachyc]ardia (VT) or VF in the acute phase have [longer] QT_c intervals on admission (4) Further[more] QT interval prolongation at discharge from [hospit]al may also predict future cardiac events and sudden deaths within the first six months in patients with AMI (3)

As a beneficial effect of treatment with β receptor blocking agents has been reported on survival in AMI patients (14 26) and as these drugs seem to shorten the QT_c interval (15 22 24) we decided to analyse the effect of long term β receptor blockade on QT_c intervals during a one year follow up of AMI

PATIENTS AND METHODS

To be included in the study the patients had to be below 70 years of age to be in sinus rhythm at discharge and to show no evidence of complete bundle branch block severe heart failure hypotension or bronchial asthma From May 1977 to Dec 1978 111 consecutive patients with AMI were discharged alive from the hospital and included in the study There were 88 men mean age 60 years (range 44–69) and 23 women mean age 58 years (range 46–69) Details concerning catchment area and routines of the unit have been published elsewhere (6) Salient clinical data were registered by code on special charts and transferred to punch-cards for computer analysis (9) Prior to discharge the patients were stratified and randomized Placebo or metoprolol 100 mg b i d were given double blindly to 52 and 59 patients respectively

Stratification was based on 1) Infarction size estimated by enzyme maximum of LD_1 (thermostable fraction LD and LD_2 of lactodehydrogenase) $LD_1<20$ µkat/l small infarction $LD_1\geq20$ µkat/l = large infarction 2) Type of ventricular arrhythmias registered on a six hour ECG three hours at day time with moderate exercise three hours at night time (16) 3) Age (below 65 years and 65 years or more)

Abbreviations QT =corrected QT interval MI=myocardial infarction AMI=acute MI VF=ventricular fibrillation VT=ventricular tachycardia

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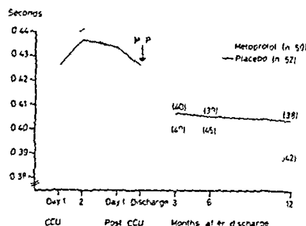


Fig 1 Mean QT_c interval in patients given metoprolol or placebo after AMI

After discharge the patients were seen regularly in the Out Patient Clinic They were readmitted for six hours ECG recording and laboratory investigations 6 and 12 months after the acute event End points were reinfarction or sudden death

Seventeen patients were withdrawn from the study due to side-effects or a need of β blockade to control deteriorating angina pectoris Of the ten patients who died during the follow-up year seven (3 on metoprolol 4 on placebo) died suddenly five of them within three months One of the patients who died suddenly had suffered a reinfarction prior to death One patient died of lung cancer Nine patients (4 on metoprolol 5 on placebo) suffered ten reinfarctions fatal in two cases In six of the patients the reinfarction occurred within three months

The QT_c intervals were measured retrospectively by one of us (S A) without knowledge of the patients clinical data QT_c intervals were calculated on seven occasions on the first two days in the CCU on the first day after discharge from CCU at discharge from hospital prior to randomization and at 3 6 and 12 months after the infarction From a 12 lead resting ECG recorded at a speed of 50 mm/sec the QT and RR intervals were measured in 3–5 consecutive beats These values were averaged and the QT was calculated from the mean according to Bazett s formula (5 13)

$$QT_c = \frac{QT}{\sqrt{RR}}$$

The measurement was made in the lead with the longest QT interval Care was taken not to measure intervals preceded by premature beats or to include U waves in the QT interval The QT interval was measured in hundredths of a second from the beginning of the QRS complex to the end of the T wave where its hind limb joined the bare line Differentiation between T and U waves or some other potential was usually possible in at least one lead If this was not possible the QT interval was measured from the beginning of the QRS complex to the notch between the T and U waves (13)

Definitions

Acute myocardial infarction was diagnosed [...] conventional criteria (1 18) *Left heart failu[re]* [...] nosed by the presence of basal pulmonary [...] monary vascular congestion on X ray *Infa[rction]* [...] terior if the ECG criteria for infarction were p[resent in two] or more of leads V_2–V_4 lateral if in two or mo[re of] aVL V_5 and V_7 and inferior if in two or more [of II] III and aVF Combination sites were determ[ined accord]ing to the same criteria In the following [...] anterolateral sites are classified as anterior [...] lateral sites as inferior *Sudden death* was defi[ned] within two hours after onset of the final sym[ptoms] *endocardial infarction* ST T changes only wi[th] enzyme pattern *Transmural infarction* [...] pathological Q wave (18) in at least two of 1[...]

Statistical methods

Conventional statistical methods were use[d] [...]nificance of differences between the mean Q[...] patient group was tested by Student s t-test

RESULTS

QT_c interval in relation to time elapsed [...] AMI and to metoprolol therapy (Fig 1)

The longest QT_c mean was registere[d] [...] second day in the CCU whereafter the [...] vals decreased QT_c intervals did not [...]nificantly on any occasion during the [...] period between patients subsequently gi[ven meto]prolol or placebo QT intervals decre[ased sig]nificantly in both treatment groups betw[een dis]charge and the three month control [...] Throughout the follow up period pat[ients on] metoprolol had significantly shorter Q[T inter]vals than those on placebo (0 394±0 [...] 0 406±0 034 sec (mean ± S D) $p<0.001$[...] metoprolol group there was a further dec[rease of] QT_c intervals between the 3 and 12 mon[th follow] up (0 398±0 025 vs 0 387±0 023 sec [...] which was not seen in the placebo group

As expected the heart rate decreased sig[nificant]ly in the metoprolol group between discha[rge and] the 3 month follow-up (74±16 vs 61±9 be[ats/min] $p<0.001$) while it remained constant in the [placebo] group (73±14 vs 73±13 beats/min) Betw[een 3] and 12 month follow up a further decreas[e in heart] rate was observed in the metoprolol grou[p ...] vs 56±6 beats/min $p<0.05$) but not in the [placebo] group (73±13 vs 69±13 beats/min N S)

1 *Mean QT_c interval (sec) in relation to type and site of infarct*

·retoprolol P = placebo

	Drug	No of pats	Before drug (days) CCU 1	2	Post CCU 1	At discharge	p	On drug (months after discharge) 3	6	12
of infarct										
..mural	M	48	0 432	0 444	0 430	0 423	<0 001	0 400	0 398	0 385
	P	38	0 425	0 438	0 434	0 431	<0 01	0 406	0 403	0 403
docardial	M	6	0 432	0 440	0 433	0 405	N S	0 385	0 400	0 390
	P	10	0 424	0 441	0 430	0 422	N S	0 413	0 429	0 420
tain	M	5	0 436	0 424	0 436	0 405	N S	0 377	0 397	0 400
	P	4	0 438	0 413	0 445	0 460	N S	0 400	0 387	0 383
infarct										
or	M	22	0 433	0 445	0 435	0 423	<0 05	0 398	0 395	0 388
	P	22	0 422	0 443	0 442	0 437	<0 05	0 409	0 408	0 412
	M	26	0 432	0 445	0 427	0 420	<0 01	0 399	0 397	0 383
	P	19	0 426	0 428	0 423	0 425	N S	0 409	0 407	0 407
	M	11	0 429	0 427	0 431	0 414	N S	0 394	0 405	0 393
	P	11	0 434	0 440	0 436	0 432	N S	0 399	0 404	0 386

nificant difference between 3- 6- and 12 month control unless otherwise stated
·05

site and size of infarct and complications

own in Tables I and II QT_c intervals de d similarly between discharge and the 3 control in the various subgroups The de in QT however was more pronounced and d a higher level of significance in relation to parameters of the metoprolol group i e turality inferior or small infarcts (LD,<20) left heart failure and in the subgroup with in the CCU

hmias

was no significant association between QT_c ls and the incidence and type of ventricular beats as registered by telemetry prior to nization or at the 6 and 12 month control in the metoprolol or placebo group

es in QT_c intervals in relation to QT_c at discharge (Table III)

ents with short QT_c intervals (≤0 420 sec) at rge no further significant decrease in QT_c gistered at the 3 month control In contrast a ant decrease between these two occasions gistered in patients with intermediate QT_c intervals (0 430–0 440 sec) in the metoprolol group but not in the placebo group In patients with long QT_c intervals (>0 440 sec) there was a significant decrease in both groups between discharge and the 3 month control In the metoprolol treated patients with QT_c intervals above 0 440 sec a further sig

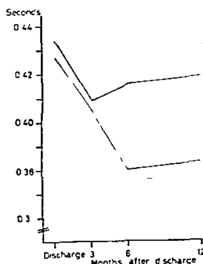


Fig 2 Mean QT interval after AMI in relation to therapy with metoprolol (*M*) or digitalis (*D*)

Table II *Mean QT_c interval (sec) in relation to size of infarct and CCU complications*
M = metoprolol P = placebo

	Drug	No of pats	Before drug (days) CCU 1	CCU 2	Post CCU 1	At discharge	p	On drug (months after) 3	6
Size of infarct									
LD_1<20	M	39	0 429	0 439	0 429	0 413	<0 05	0 398	0 39[illegible]
	P	31	0 425	0 445	0 433	0 426	N S	0 410	0 41[illegible]
LD_1≥20	M	20	0 438	0 447	0 435	0 434	<0 001	0 397	0 39[illegible]
	P	21	0 427	0 425	0 435	0 440	<0 001	0 401	0 39[illegible]
CCU complications									
Left heart failure	M	37	0 437	0 444	0 433	0 424	<0 001	0 394	0 39[illegible]
	P	40	0 431	0 439	0 434	0 431	<0 01	0 409	0 40[illegible]
No left heart failure	M	22	0 424	0 438	0 426	0 413	N S	0 404	0 40[illegible]
	P	12	0 408	0 429	0 436	0 433	N S	0 400	0 40[illegible]
VT	M	19	0 436	0 439	0 434	0 420	<0 01	0 390	0 401
	P	20	0 429	0 434	0 453	0 436	<0 01	0 407	0 40[illegible]
No such arrhythmias	M	40	0 430	0 443	0 429	0 420	<0 01	0 401	0 396
	P	31	0 425	0 440	0 422	0 429	<0 05	0 407	0 409

No significant difference between 3 6- and 12 month control

nificant decrease was however registered between the 6 and 12 month controls (Table III)

In the metoprolol group a significant decrease was noted in heart rate between discharge and the 3 month control within the three subgroups with QT_c intervals above 0 410 sec (p<0 05 p<0 01 p<0 05) No further significant decrease was seen in these subgroups between the 3 and 12 month control No significant change in heart rate was registered in the placebo group

QT_c intervals in patients with or without digitalis therapy (Fig 2)

Thirty patients in the metoprolol group and placebo group were not on digitalis at dis during the follow up The corresponding of patients on digitalis during this period and 11 The remaining patients were on th for shorter periods or intermittently

QT_c intervals decreased significantly discharge and the 3 month control in pa

Table III *Mean QT_c interval (sec) in subgroups within different QT_c limits at discharge*
M = metoprolol P = placebo

QT_c at discharge	Drug	No of pats	Before drug at discharge	p	On drug (months after discharge) 3	6	12
<0 400	M	18	0 384	N S	0 397	0 382	[illegible]
	P	14	0 390	N S	0 395	0 395	[illegible]
0 410–0 420	M	14	0 411	N S	0 392	0 399	[illegible]
	P	10	0 414	N S	0 405	0 403	[illegible]
0 430–0 440	M	14	0 434	<0 01	0 404	0 404	[illegible]
	P	11	0 436	N S	0 422	0 416	[illegible]
>0 440	M	13	0 464	<0 001	0 401	0 406	[illegible]
	P	17	0 473	<0 001	0 408	0 417	[illegible]

No significant difference between 3 6- and 12 month control unless otherwise stated
* p<0 05

rolol w th or without d gital s ($p<0.01$) This rue al o for pat ents without d g tal s in the group ($p<0.05$) During the follow up s on bo h metoprolol and dig tal s had sig ntly shorter QT intervals than those on rolol only (0 378+0 031 vs 0 404+0 071 01) S m larly in the placebo group patients pta had s gn f cantly shorter QT intervals the follow up (0 390+0 021 vs 0 414+0 029 <0 01)

a ents on metoprolol only there was a s g nt decrease in QT intervals between d s and 3 month control among pat ents with m s of 0 430 0 440 sec and above 0 440 t d scha ge (0 434+0 005 vs 0 413+0 015 <0 05 and 0 464+0 011 vs 0 409+0 018 <0 001 respect vely) In the correspond ng o group th s was true for pat ents w th mean bo e 0 440 sec (0 474+0 071 and 0 419+0 0 9 <0 01)

ter als n pat ents tl s bseq ent ca diac e ents

pa ients who subsequently d ed suddenly had can ly longer QT intervals than those with ajor card ac events at d scharge and prior rapy (0 453+0 057 vs 0 473+0 035 sec 5) Two of these pat ents were on digital s and as also on quin d ne at discharge

ntervals n those 9 who suffered reinfarct on n ermed ate (0 477+0 040 sec) and d d not s gnif antly from the QT ntervals of those ed suddenly or who had an uneventful re F e of the pat ents who suffered a re n n we e on d gital s and another on both ine and d gital s

sta tical analysis was performed at the 3 control of pat ents who suffered major car ven s as most of these events had already ed w thin th s period

DISCUSSION

longed QT in erval n pat ents with prev ous mes an ncreased risk of sudden death (21) so of e nfarct on (3) In accordance with pre studies (3 7) we found QT_c prolongat on dur acute phase of an AMI in our pat ents and a d decrease at subsequent measurements In e ious studies there are nd cat ons that the se erely ll MI patients tend to have longer QT intervals (? 3 4) During the acute pha e of an infarction QT prolongation may be due to lo al hypotherm a (8 13) or hypocalcem a (13 23) QT interval prolongation may to some extent also d pend on increase in or imbalance of the sympathe nervous system (20) It is known from an mal e periments that ablat on or blockade of the left and right stellate gangl on w ll result in a marked s and decrease respect vely in the V F thre ho d 20) and also influence the QT nterval right stellectomy w ll prolong the refractory per ods on the anter or card ac wall and left stellectomy ma nl on the posterior ventricular wall (27) As QT pro longat on seems to be a common featur in MI pat ents w ho develop ventricular f brillation (10 or subsequent sudden d ath (21 a po ble therapeutic approach would be to try to decrea e sympathetic tone and hereby shorten th in r al This has indeed been a h eved h prom s ng re sults with β block ng agen s n th hered tary long QT_c syndromes (11 17 19 5) A b nef c al effect of β blockade on mortal ty h l o b n epo rt d n stud es of pat ents af er an AM (14 26 Po b e mechan sms beh nd th pre en e c n are ll be ng d scussed and n es gate

Acute adm n strat on of β b k n h ens QT ntervals (? 24 Nyberg et a l e tered the same effect on QT n er al unr term therapy with alpreno ol The re ult that the decrease in QT nterval wa m nounced in the most severely ll pat nt these pat ents had the h ghest mea Q treatment In agreement w th the e r e found the shortening effect of β block de n Q be most marked n those i h pro ged QT tervals at d scharge Th s reduct anno h expla ned by other drugs influenc ng th QT val i e d gitalis (?) as these f nd ngs we e al o obtained in patients not on d gital s

We also looked at QT_c interval changes in re lat on to type s te and size of infarct CCU com pl cat ons and ventricular arrhythmias reg stered by telemetry prior to random zat on and at the 6 and 12 month controls However n th s prospect e study which is st ll in the sampl ng stage the number of pat ents n these subgroups is too small to allow any conclus ons about a probable be nef cial clin cal effect of β receptor blockade or whether such an effect is related to changes in QT intervals

A find ng n a prev ous study (3) was conf rmed

here namely that patients dying suddenly during the first follow up year have longer QT_c intervals at discharge than those without major cardiac events. The proposed beneficial effect of β receptor blockade on QT_c interval in this group of patients can not be evaluated as most of these patients had died before the first control. A report will follow on these patients in a future follow up study.

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REFERENCES

1. Ahnve S. Non infarction cases without previously known ischemic heart disease admitted to a coronary care unit. Eur J Cardiol 9/4: 307, 1979.
2. Ahnve S, Helmers C & Lundman T. QT_c intervals at discharge after acute myocardial infarction and long term prognosis. Acta Med Scand 208: 55, 1980.
3. Ahnve S, Helmers C, Lundman T, Rehnqvist N & Sjögren A. QT_c intervals in acute myocardial infarction. A one year follow up. Clin Cardiol. To be published.
4. Ahnve S, Lundman T & Shoaleh var M. The relationship between QT interval and ventricular arrhythmias in acute myocardial infarction. Acta Med Scand 204: 17, 1978.
5. Bazett H C. An analysis of the time-relations of electrocardiograms. Heart 7: 353, 1920.
6. Biörck G, Lundman T, Mogensen L & Orinius E. Experience from a coronary care unit. Arch Klin Med 216: 242, 1969.
7. Doroghazi R M & Childers R. Time related changes in the Q T interval in acute myocardial infarction: possible relation to local hypocalcemia. Am J Cardiol 41: 684, 1978.
8. Emslie Smith D, Sladden G F & Stirling G R. The significance of changes in the electrocardiogram in hypothermia. Br Heart J 21: 343, 1959.
9. Hall P, Lundman T & Nordlander R. Computerized case records in a cardiac infarction ward. Läkartidningen 70: 4305, 1973.
10. Haynes R F, Hallstrom A P & Cobb L A. Repolarization abnormalities in survivors of out-of hospital ventricular fibrillation. Circulation 57: 654, 1978.
11. Jervell A & Lange Nielsen F. Congenital deaf mutism, functional heart disease with prolongation of the QT interval and sudden death. Am H[...] 59: 1957.
12. Kliks B R, Burgess M J & Abildsko[...] Influence of sympathetic tone on ventric[...] lation threshold during experimental [...] occlusion. Am J Cardiol 36: 45, 1975.
13. Lepeschkin F. Modern electrocardiograph[...] Williams & Wilkins, Baltimore 1951.
14. A multicentre International Study. Impro[...] prognosis of myocardial infarction by [...] beta adrenoreceptor blocking using practolo[...] J 3: 735, 1975.
15. Nyberg G, Vedin A & Wilhelmsson C. [...] patients treated with alprenolol or plac[...] myocardial infarction. Br Heart J 41: 45[...] 19[...]
16. Rehnqvist N. Ventricular arrhythmias afte[...] myocardial infarction. Prognostic weight an[...] history. Eur J Cardiol 7/2-3: 169, 1978.
17. Romano C, Gemme, G & Pongiglione R. [...] cardiache rare dell età pediatrica. II. Acce[...] pali per fibillazione ventricolare parossisti[...] Pediatr 45: 656, 1963.
18. Rose C & Blackburn H. Cardiovascula[...] methods. WHO Geneva 1968.
19. Schwartz P J, Periti M & Malliani A. [...] Q T syndrome. Am Heart J 89: 378, 1975.
20. Schwartz P J, Snebold N G & Brown[...] Effects of unilateral cardiac sympathetic de[...] on the ventricular fibrillation threshold. Am [...] 37: 1034, 1976.
21. Schwartz P J & Wolf S. Q T interval pro[...] as predictor of sudden death in patients with[...] dial infarction. Circulation 57: 1074, 1978.
22. Seides S F, Josephson M E, Batsford [...] Weisfogel G M, Lau S H & Damato [...] electrophysiology of propranolol in man. Am [...] 88: 733, 1974.
23. Shen A C & Jennings R B. Kinetics of [...] accumulation in acute myocardial ischemi[...] Am J Pathol 67: 441, 1972.
24. Stern S & Eisenberg S. The effect of pro[...] (Inderal) on the electrocardiogram of normal [...] Am Heart J 77: 192, 1969.
25. Ward O C. A new familial cardiac synd[...] children. J Irish Med Ass 54: 103, 1964.
26. Wilhelmsson C, Vedin J A, Wilhelm[...] Tibblin G & Werkö L. Reduction of sudden [...] after myocardial infarction by treatment [...] prenolol. Lancet 2: 1157, 1974.
27. Yanowitz F, Preston J B & Abildskov [...] Functional distribution of right and left stel[...] vation to the ventricles: production of ne[...] electrocardiographic changes by unilateral a[...] of sympathetic tone. Circ Res 18: 416, 1966.

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Enzyme Activities in Serum after Extensive Exercise, with Special Reference to Creatine Kinase MB

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TRACT It is well documented that elevations of n enzymes used as criteria in establishing the nosis of acute myocardial infarction (AMI) often a pattern of AMI after physical exercise with ther clinical signs of myocardial damage Since a al condition resembling AMI sometimes appears strenuous physical exercise, this study was de d to show if the new almost heart specific nzyme creatine kinase MB (CK MB) would solve diagnostic problems Ten well trained volunteers part in a 26 km jogging race None of them had cardiovascular symptoms, but the old cardiac mes rose in some of them above the discrimina levels whereas CK MB was below these levels in ases It is concluded that CK MB determination valuable diagnostic tool also in patients who have ntly exercised extensively

words creatine kinase MB exercise acute myocar infarction diagnosis

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ermination of serum lactate dehydrogenase 1 1 1 27 LD) aspartate aminotransferase (EC 1 1 ASAT) and creatine kinase (EC 2 7 3 2 has been widely used in the diagnosis of acute cardial infarction (AMI) Recently the reliabili f the diagnosis of AMI has improved by meas ment of the isoenzyme MB of CK (CK MB) the erto most sensitive and specific indicator of I (5) Few investigators have demonstrated d CK MB levels in patients with skeletal mus

viations AMI = acute myocardial infarction LD ctate dehydrogenase ASAT = aspartate aminotrans e CK = creatine kinase CK MB = isoenzyme MB K

cle diseases (8 12) or hypothermia (2) without AMI Their findings can be explained by the small amounts of CK MB found in skeletal muscle (4 7) However these disorders rarely complicate the dif ferential diagnosis of AMI so they are of minor clinical importance In contrast the increasingly popular sport of jogging sometimes involves a clini cal condition resembling an AMI (1 6)

As conclusions based on determinations of serum LD ASAT and CK after physic exercise are con troversial the pattern found sometimes r sembling that of AMI (3 6) these enzymes are not suitable for ruling out the presence of this di ea e The principal aim of the present study was to eluc date whether determination of serum CK soenzyme could redress this confusion

SUBJECTS AND METHODS

Ten volunteers completing a 26-kilometer jogging ra (Mølleåløbet) participated in the study Their clinical data are presented in Table 1 Their level of training is ndi cated by the number of km they have been runn ng n the month before the race

Table I *Participants in the 26 km long jogging race*

Subj no	Age (y)	Sex	Years of training	Km run in the month before the race
1	12	♂	4	100
2	18	♀	5	150
3	21	♂	15	50
4	33	♀	6	150
5	37	♂	25	55
6	43	♀	4	145
7	46	♂	7	150
8	50	♀	8	150
9	53	♂	10	100
10	74	♀	15	300

Table II *E ι \n e actι t es (μkat/l) before j st after 4 8 and 20 l o rs after l g d stanc j gg ng and range)*

	Before	Just after	4 h after	8 h after	20 h after
CK MB	0 (0–0 1)	0 07 (0–0 25)	0 13* (0–0 37)	0 23** (0–0 47)	0 18 * (0–0 33)
Total CK	2 45 (1 05 3 95)	3 90* (1 52 5 93)	6 38* 1 5? 14 43)	8 57** (1 5? ?1 17)	7 38 (1 75 21 00
ASAT	0 38 (0 27–0 88)	0 5? ⁸ (0 25–0 9?)	0 50^NS (0 25–0 80)	0 60* (0 27–0 82)	0 57 ⁸ (0 27–0 93)
LD	5 10 (4 35–6 83)	7 93** (5 6–13 0)	6 78* (4 60–9 75)	6 8 ** (5 ?8 9 10)	6 28 (5 55–8 9?)

Levels of s gn f cance as compared w th n t al values (Student s *t* test) ^NS $p>0.05$ * $p<0.05$ ** $p<0.01$

Venous blood was sampled at rest w th n one hour before just after and 4 8 and ?0 hours after the race The serum was frozen and stored at 20°C pend ng analys s wh ch was performed with n 7? hours LD ASAT and CK were assayed on unhemolysed serum accord ng to the Scand nav an recommendat ons (9 10) CK soenzyme rat os were determ ned by electrophores s w th fluores cence scann ng of the electropherogram (4) The upper reference levels of serum act vι es based on discrim na tory analys s for pat ents w th and w thout AMI were LD 6 68 μkat/l ASAT 0 67 μkat/l CK 3 33 μkat/l and CK MB 0 50 μkat/l (5)

RESULTS

Table II shows the mean enzyme activit es in the ten volunteers as functions of t me A s gn f cant in crease was observed in each of the four enzymes *The mean levels of CK MB and total CK had peak* values 8 hours after the race but the mean values 20 urs after were st ll s gn ficantly h gher than the al values ASAT act vity was s gn f cantly ra sed e ght hours after the race LD activit es were s gnif cantly ra sed in all postexerc se measure ments The mean hematocrit value was 0 43 before and after the race suggesting an unchanged plasma volume

There was no correlation between the increas ng serum enzyme activit es and the part c amount of tra n ng It is obv ous from Table l when the d scr minatory levels of the four en were used CK MB led to no false pos ve n wh le the three old enzymes y elded l 7 fals t ve f ndings

DISCUSSION

The present investigat on conf rms the well k fact that the serum activit es of ASAT LD an CK rise after exercise (3 6 11) During the the pattern of CK MB was s m lar to the tot *pattern S nce trace amounts of CK MB are* in skeletal muscle (4 7) and the molecular w and d stribut on spaces of CK MB and total C *virtually ident cal it is l kely that* the small am of CK MB found in serum orig nate from sk muscle but the heart can of course not be ex as a part al source

The fact that the d fferent levels of tra ning part c pants d d not correlate with the pos serum enzyme levels indicates *that* corresp results m ght be seen in untra ned persons as

None of the part c pants in the present stud any cl n cal s gns of AMI after the con

Table III *N n ber of part cιpa ts ıl sere m en ȝn e act t es l gher tl an the d scrım naton level*

	Before the race ($n=10$)	Just after (n 10)	4 h after (n 9)	8 h after (n 9)	20 h after ($n=7$)
CK MB	0	0	0	0	0
Total CK	2	7	7	7	5
ASAT	1	2	3	3	2
LD	1	5	4	4	3

cal exert on performed Patients with exer nduced symptoms of AMI are sometimes ad d to coronary care un ts If these pat ents do ave AMI determ nation of the old enzymes ead to false pos t ve results whereas our find uggest that serum CK MB determinations w ll 10 false pos tive results

ACKNOWLEDGEMENTS

s udy was supported by grants from Idrættens nmg råd (The Dan sh Sports Research Council) the h Heart Foundat on and A/S Nord sk Gjenfors kr ngs ibs Jub æumsfond

REFERENCES

rg A & Haralamb e G Changes in serum ea ne k nase and hexose phosphate isomerase ac y w h exerc se durat on Eur J Appl Phys ol 191 19 8

irlson J C Em lson B & Rapaport E Creat ne 10 phok nase MB isoenzyme n hypotherm a Case ports and experimental stud es Am Heart J 95 352 78

Bahme R A Kazantz s A Luch R J Raizner E & Gyorkey F Effect of rout ne treadm ll test g on the serum enzyme Card ology 61 162 1976

rande P Chr st ansen C & Næstoft J Creat ne k nase soenzyme MB assay by electrophore s Scand J Cl n Lab Invest 39 607 1979

5 Grande P Christ ansen C Ped rsen A & Chr tensen M S Opt mal d agnos s n acu e mvoca d infarct on A cost effectiveness study C rculat on 6 7?3 1980

6 Schnohr P Enzyme concentra ons n serum afte prolonged phys cal exerc e Dan Med Bull 1 69 1974

7 Sm th A F Separat on of t ssue and serum c eat ne k nase isoenzymes on polyacrylam de gel slabs Cl n Ch m Acta 39 351 197?

8 Somer H Dubowitz V & Donner M Creat ne k nase soenzymes n neuromuscular d ease J Neurol S 1?9 1?9 1976

9 The Comm t ee on Enzymes of the Scand n an Soc ety for Cl n cal Chem stry and Cl n cal Phy olo- gy Recommended method for the determ na on of four enzymes in blood Scand J Cl n Lab Inve 33 ?90 19 4

10 — Recommended method for the dete m nat on of creat ne k nase n blood mod fed by the nclus on of EDTA Scand J Cl n L b In est 39 1 1979

11 Vejjaj va A & Teasdale G M Serum cr a ne k nase and phys cal exerc e B Med J 1 1653 1965

1? Yasm neh W G Ibrah m G A Abbasnezhad M & Awad E A Isoenzyme d ribu on of crea ne k nase and lactate dehyd oge se n erum and skeletal muscle in Duchenne mus ular d o hy col lagen d sease and other muscular d de s Cl n Chem 24 1985 1978

BOOK REVIEW

Ass sted C rculat on ed ted by Fel x Unger 653 pages US$ 110 Spr nger Verlag Berl n He delberg and New York 1979

This book deals with all types of ass sted c rculat on from the s mplest k nd of counter pulsat on to art f c al heart and heart transplantat on H stoncal background d ffer ent techn cal dev ces experimental and cl n cal results compl cat ons energy sources etc are carefully de scnbed in 10 ma n parts each part composed of contribu t ons from several internat onal authors

Part I deals w th counter pulsat on external counter pulsat on as well as ntra aort c balloon pump ng Ind ca t ons cl n cal results and compl cat ons are reported More than 10 years experience ex st now n the f eld of co inter pulsat on n assoc at on w th acute myocard al infarct on as well as card ac surgery

Part II s the most extens ve part of the book nclud ng almost 200 pages about left ventricular ass stance dev ces to be used temporar ly postoperat vely or for totally n *tracorporeal implantat on and long term assistance (1-?* years) wh le wa t ng for heart transplantat on A great deal of the contribut ons describes d fferent devices and tech n cal solut ons that have been tested mostly n the experi mental s tuat on and in some cases also n cr t cally ill pat ents Of spec al nterest is the sect on deal ng w th comb ned right and left heart ass stan e wh cl be more effect ve n the treatment of card o where r ght ventricular fa lure of va ous deg mon Th s is also po nted out by Åke Senn chapter of the book

Parts III and IV descr be *the total art fc* heart transplantat on where the Stanford Gr ports a 3 year surv val of 60% after heart tran

Parts V and VI are techn cal chapters d fferent aspects of the driv ng systems b on *art f c al val es*

The conclud ng parts of the book nclude current l terature during the last 4 years a d a chapter Horizons on the future trends n as t on

It is imposs ble to review all the con nt volume of th s s ze wh ch ncludes so much However it must be stated that the volume a excellent It prov des interest ng and easy r chly illustrated (3?? f gu es and 73 tables recommended for those work ng n the f eld c rculat on n the coronary care un t or n as o heart surgery and t can also serve as a valuab volume

Olof N q st Stockholm

Acta Med Scand 208 233-236 1980

Excessive Sensitivity to the Hyponatremic effect of Chlorpropamide in a Patient with Diabetes mellitus and Anterior Pituitary Insufficiency

Gunnar Aasen and Harald M M Frey

From Medical Department B Aker Hospital University of Oslo Oslo Norway

ACT A 67 year old diabetic woman with un ed anterior pituitary insufficiency developed tremic coma within 5 weeks after initiation of opamide therapy A provocation test with 500 orpropamide orally led within five hours to tremia and sopor with high urinary sodium on This rapid development of the hyponat yndrome excludes water retention due to ADH dominant cause It is more probable that defects in renal sodium conservation, brought by the anterior pituitary failure, have been ated by chlorpropamide

rds chlorpropamide hyponatremia pituitary in ncy

ed Scand 208 233 1980

oropamide induced dilution syndrome has reported several times since the first case re 1970 (13) It was present in 4% of patients iabetes mellitus treated with chlorpropamide The mechanism is not fully understood but ice suggests enhancement by chlorpropamide antidiuretic action of vasopressin in the kid 16 17 18 30) The ensuing diluting syn is indistinguishable from the syndrome of ropriate secretion of antidiuretic hormone DH) due to other causes mainly bronchogenic noma chest infections (24) different central ous system disorders and miscellaneous drugs yponatremia in SIADH is due to extracellular expansion and secondary sodium loss (5)

is report describes severe hyponatremia dur treatment with chlorpropamide in a patient diabetes mellitus who in addition suffered anterior pituitary insufficiency Hyponat a is frequently present in hypopituitarism due adequate secretion of both glucocorticoids and ralocorticoids (3 6 7 11 14 15 21 27) Lack of thyroxine (2 8 9 10 28) ad growth hormone are also of importance

CASE REPORT

A 67 year-old woman with diabetes mellitus since 1970 was placed on chlorpropamide therapy 50 mg daily on July 6 1977 Within the first weeks of treatment she subsequently developed nausea [illegible] ability reduced memory and fatigue On Aug 7 vomiting occurred and she became soporous On the next day she was admitted to Medical Department B Aker Hospital She appeared well hydrated without edema A few ho [illegible] she became comatose with general convulsion and [illegible] plantar reflexes Cerebrospinal fluid was [illegible] normal pressure

Laboratory examination revealed Hb [illegible] hematocrit 0 40 blood urea 5 mmol/l blood g [illegible] mmol/l serum sodium 103 mmol/l serum [illegible] mmol/l serum chloride [illegible] mmol/l serum [illegible] mmol/l urine osmolality 494 mmol/l Acid b [illegible] was nearly normal with pH 7 40 pCO 4 [illegible] bicarbonate 21 5 mmol/l and base defi [illegible]

Chlorpropamide and water ingestion were [illegible] and infusion of mannitol and hypertonic [illegible] started (Table I) Blood pressure was then [illegible] during infusion to 130/80 Renin activit [illegible] aldosterone concentration (196 pmol/l) in peripheral [illegible] were within normal limits

Clinical improvement with returning consciousness ensued parallelling the elevation of serum sodium during saline infusion Some degree of hyponatremia persisted (mean 130 mmol/l) during the following days with hypertonic urine relative to plasma when on oral water restriction of 750 ml/day and a diabetes diet of 2 000 kcal containing approximately 80 mmol/l of sodium daily Treatment with slow acting insulin 12 IU daily was also initiated Serum concentration of chlorpropamide was 189 μmol/l on admission after 3 days 78 on the 4th day 49 and on the 7th day 16 5 μmol/l To determine her renal diluting capacity an oral water load of 20 ml/kg was given on the 7th day showing insufficiency of maximal urinary dilution (less than 100 mOsm/kg) and delayed excretion (only 50% excreted within 4 hours) Some urinary dilution did however occur and the whole water load was eventually excreted Continued water loading on the same and on the following 2 days gave confirmatory results (Table II)

Table I *Status on admiss on Aug 8 1977 and response to therapy*

Hour	Serum Na (mmol/l)	Osmolal ty (mOsm/kg) Serum	Urine	Urinary Na (mmol/l)	Diures s (ml/2 h)	Natri ures s (mmol/2 h)	Therapy
17	103	215	494				
20							Mannitol 75 g v (500 m 42 mM 2 9 NaCl (00 m
22	96	225	472	10	755	8	Mann tol 37 g v (50 ml
24	103	23?	466	8	740	6	210 mM 2 9% NaCl (500 m
02	110	241	538	4	350	1	210 mM 2 9% NaCl (500 m
04	119	244	561	39	250	10	
06	121	247	612	97	90	9	105 mM 2 9% NaCl (250 ml
08	125	248	669	60	8?	5	
Total					2 267 ml/ 12 h	39 mmol/ 12 h	2 100 ml H O 567 mM Na

Further assessment of renal funct on revealed no ab normality Serum creat n ne was 65 μmol/l maximal urinary concentrat on 948 mOsm/kg renal isotope scan was normal with normal effect ve renal plasma flow b laterally Glomerular f ltrat on rate was 130 ml/ m n × 1 73 m² Adrenal funct on judged by plasma cortisol ind cated normal d urnal values (685 and 435 nmol/l) at that t me

X-ray of the skull and sella turcica was normal A com putertomogram revealed some central and cort cal bra n atrophy EEG showed organic alterations with a max mum in the left fronto temporal region wh ch showed improvement at EEG control two weeks later

To assess the role of chlorpropam de a provocat on test with 500 mg orally was performed on Aug 19th The pat ent was then on Retard Insul n 12 IU da ly and her fast ng blood glucose level on that day was 11 4 mmol/l She was allowed to drink freely After a few hours she felt ill and became soporous w th n 5 hours Serum sod um was then 118 mmol/l Natriures s was remarkably h gh (333 mmol/24 h) (Table III) Serum sod um was 115 l/l on the next morn ng and the cond t on unchanged erted plantar reflexes were present Infus on w th hyperton c sal ne (2 9%) was started and consciou returned gradually after add t on of mann ol

During the next month the pat ent was n rela [illegible] cond tion but exhib ted reduced memory and [illegible] fat gue Hyponatremia w th hypertonic y of urine [illegible] to plasma was found on se eral occas ons a [illegible] cosur a d m n shed to ze o Urinary sod um los [illegible] apparent although natriures s was unusually high [illegible] 4th day after provocation w h chlorpropamide mmol/24 h) (Table III) At d scharge on Sep 19th [illegible] sod um was 140 mmol/l natriures s 230 mmol [illegible] d ures s 1930 ml/24 h Some urinary loss of sodium therefore present also when not on chlorpropam[illegible]

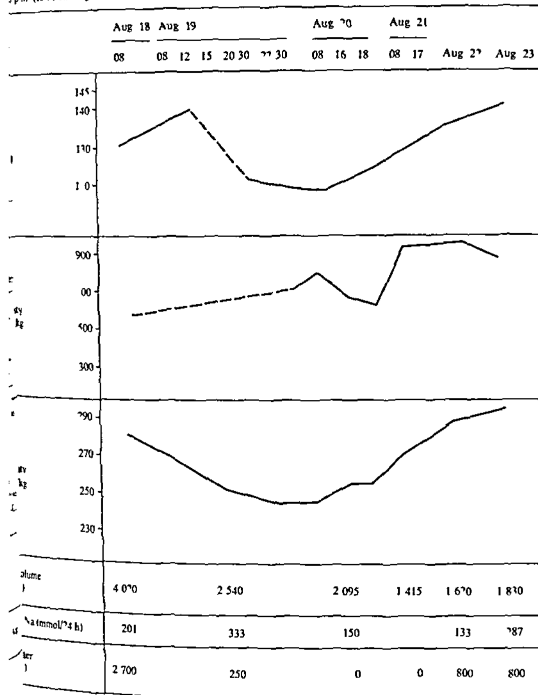
The patient s thyro d funct on was reduced [illegible] thyrox ne be ng 38 nmol/l T_3 1 0 nmol/l and TSH [illegible] Further invest gat on of her p u tary function [illegible] blunted TSH response to TRH stimulation (Table [illegible] Inderal/glucagon test showed no s gn ficant n [illegible] growth hormone level Metopiron test nd cated [illegible] tary ACTH reserve Gt RH test showed normal [illegible] but no rise in FSH Urinary 17 KGS were de[illegible] accord ng to Norymberski et al (0) and urinary [illegible] by the method of Few (12) Urinary free cort[illegible]

Table II *Water load*

20 ml/kg on Aug 15 (8 a m 9 a m) 3 000 ml/24 h on Aug 15 16 and 17

	Aug 15th 3 a m	9 a m	10 a m	11 a m	12 00	1 p m	Aug 16 th	Aug 17 th	[illegible]
Serum Na (mmol/l)	131	12?	129	130	129	123		136	[illegible]
Serum osmolal ty (mOsm/kg)	264	262	259	262	255	255			
Urine osmolal ty (mOsm/kg)		534	364	301	215	180			
Urinary Na (mmol/l)		135	78	39	27	36			
Urine volume (ml/h)		75	105	170	210	200			
Urine volume (ml/24 h)						3 750	2770	29??	[illegible]
Urine osmolal ty (mOsm/kg/24 h)						221	248	?9?	[illegible]
Body we ght (kg)	52 8						51.8	52.?	[illegible]

III *Chlorpropam de provocation*



ortisol were determ ned as described by Aakvaag) Plasma ACTH was determined follow ng the turer's protocol by a kit from the Rad ochem cal Amersham England Methods for determ nat on pituitary hormones TSH (25) prolact n (22) LH SH (26) and growth hormone (19) have been publ shed by various authors from the Hormone Laboratory Aker Hosp tal

The patient thus had partial anterior p tu tary insufficiency poss bly of hypothalamic origin She was placed on thyrox ne 0 1 mg daily and was later also g ven cort sone

Table I *Status on admission Aug 8 1977 and response to therapy*

Hour	Serum Na (mmol/l)	Osmolality (mOsm/kg)		Urinary Na (mmol/l)	Diuresis (ml/2 h)	Natriuresis (mmol/2 h)	Therapy
		Serum	Urine				
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Total					2 267 ml/12 h	39 mmol/12 h	2 100 ml H O 567 mM Na

Further assessment of renal function revealed no abnormality Serum creatinine was 65 µmol/l maximal urinary concentration 948 mOsm/kg renal isotope scan was normal with normal effective renal plasma flow bilaterally Glomerular filtration rate was 130 ml/min × 1 73 m² Adrenal function judged by plasma cortisol indicated normal diurnal values (685 and 435 nmol/l) at that time

X ray of the skull and sella turcica was normal A computertomogram revealed some central and cortical brain atrophy EEG showed organic alterations with a maximum in the left fronto-temporal region which showed improvement at EEG control two weeks later

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During the next month the patient was in rela[illegible] condition but exhibited reduced memory and [illegible] fatigue Hyponatremia with hypertonicity of urine [illegible] to plasma was found on several occasions although cosuria diminished to zero Urinary sodium los[illegible] apparent although natriuresis was unusually high [illegible] 4th day after provocation with chlorpropamide mmol/24 h) (Table III) At discharge on Sept 19th [illegible] sodium was 140 mmol/l natriuresis 230 mmol [illegible] diuresis 1930 ml/24 h Some urinary loss of sodi[illegible] therefore present also when not on chlorpropamide

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Serum osmolality (mOsm/kg)	264	262	259	262	255	255		
Urine osmolality (mOsm/kg)		534	364	301	215	180		
Urinary Na (mmol/l)		135	78	39	27	36		
Urine volume (ml/h)		75	105	120	210	200		
Urine volume (ml/24 h)						3 750	2 720	[illegible]
Urine osmolality (mOsm/kg/24 h)						221	248	[illegible]
Body weight (kg)	5[illegible] 8						51.8	[illegible]

Acta Med Scand 208 237 240 1980

Predominant B-Lymphocyte Deficiency in a Case with Lymph Node Disease Resembling Angioimmunoblastic Lymphadenopathy

Bertil Persson Alf Rausing Ingemar Turesson and Olle Zettervall

om the Departments of Med cine and Path ol gy General Hosp tal Un vers ty of Lund Malmo S eden

ACT A case with clinical and histological s resembling angioimmunoblastic lymph athy but with a very marked decrease in B ytes instead of T lymphocytes is presented

rds angioimmunoblast c lymphadenopathy lym B defic ency

ed Sca d 208 237 1980

oblast c lymphadenopathy was described in n Lukes and Tindle (5) and angioimmuno- l mphadenopathy in 1974 by Frizzera et al se terms may cover a spectrum of abnormal le react ons Very little is known about the Graft versus host reaction autoimmunity mmune B lymphocyte prol feration and ms versus virus liver extracts antiepileptics d n and sulfonamides have been discussed

MANIFESTATIONS

ost common cl n cal manifestat ons are fever s g we ght loss rash pruritus general lymph a hy and hepa osplenomegaly Laboratory tests ten characterized by h gh B lymphocyte and low hocyte numbers polyclonal hyperglobul nemia s g all immunoglobul n classes lymphopenia ometimes eosinophilia and Coombs-positive tic anem a H stolog cally a destruct on of nor aph node structure is seen There is a prol fera arborizing vessels mostly venules with high endo- and further a d ffuse infiltrat on with immuno- plasma cells and intermed ate cell forms and an tal amorphous eosinophil c material Tissue hilia is often seen The B reg ons of the nodes are or distinct

e is a h stolog al difference between the cases d by Lukes and Tindle and by Frizzera et al The had a sparse cellularity of the infiltrate while the ad a h ghly cellular p cture Th s variation in his al features may suggest the poss b lity of a tenency in cases w th the histolog cal diagnoses in quest on However the cellular type of disease may probably progress to the type with cellular depletion and it seems probable that an abnormal immune response is the common cause but there may be several subgroups Some cases are rapidly progressive with or without treatment and d e with n about 2 years Others have a better prognosis and respond with remission on either steroid or cytostatic treatment and live for 2–6 years Some authors however mean that the frequency of severe infections is h gher among patients on than off cytostat c treatment (2)

Eosinoph l a is regarded prognost cally favourable A number of patients possibly as many as 10–20% develop mal gnant lymphoma (4) but most die in infections A case with a h stolog cal diagnosis of ang oimmunoblastic lymphadenopathy (AILD) but predominantly B lymphocyte deficiency is reported below

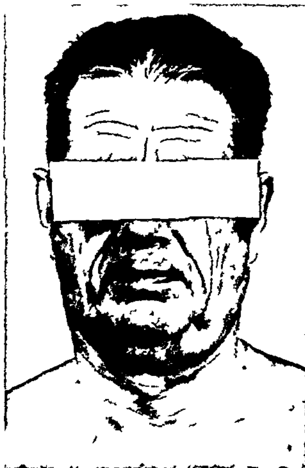
CASE REPORT

A man born in 1908 has a heredity for Mb Park nson He is a mechanic and has had a sl ght exposure to asbestos He has two healthy ch ldren

Hypertension (200/100) was noted in 1972 In the same year a progressive Mb Parkinson with pronounced tremor began to develop He was treated with d goxin hydrochlorothiazide levodopa and amantad ne In March 1978 when changing one brand of levodopa to another both w th decarboxylase antagonists he noted pruritus and in Nov an itching skin rash ch lls and lymph node swellings in the right inguinal reg on

On adm ssion to the hosp tal in Dec 1978 he had massive lymph node swell ng in the axillae supraclavicularly and inguinally and in the neck (F g 1) Scintigraphy showed splenomegaly

ESR was sl ghtly increased (40 mm/h) and platelet counts were constantly low (77 9? 10⁹/l) white cell count was normal (7 9 10⁹/l) and relative lymphopen a (16%) was constant Eosinophil a (total eosinoph l count about 800 10⁶/l) high levels of IgG (76 g/l) and IgM (9 6 g/l) and a catodal IgG band (3 g/l) were present Sternal bone marrow smears showed a sl ght increase in plasma cells Coagulation status showed an increase in factor VIII Immunological tests showed IgM ant bod es (1/64 t tre) against striated muscle and glomeruli and borderl ne value in acryl f xat on test (1/40 titre)



F g 1 Mass ve swell ng of lymph nodes before treatment w th predn solone

V rus isolat ons showed herpes s mplex n the ... He had constant serolog cal t ers fo cytomeg... rubella and influenza A No abnormal es were rep... n sk n sens t v ty tests Coombs tes bacteriol... tures and ba teriolog cal serology thyroid func... ney funct on leucocyte phagocyt func on and leu... m grat on

H stology

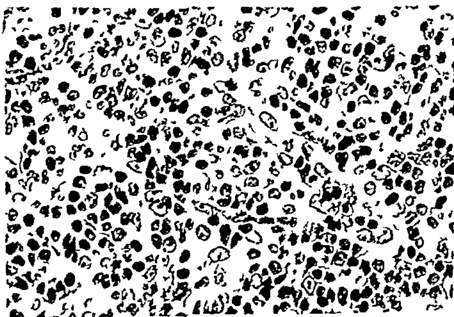
The h stolog cal p cture was that of the cell-rich ty... AILD described above (F gs 2 and 3) A fair num... plasma cells were p esent There was infiltration... same type of t ssue through the lymph node caps... the surround ng fatty t ssue The lymph node wa... interpreted by Henry Rappaport w hou access t... cl n cal data and he states that the pronounced a... vascular prol ferat on suggests AILD However... character st c features of AILD such as the pres... large numbers of plasma cells are lacking In th... has observed s m lar non-d agnost c fea ures whi... cede the development of the typ cal h s ological fe... of AILD (2)

Therapy

The pat ent was trea ed w h predn solone in a... dose of 60 mg da ly w th a success e decrease to... da ly after 2 months There was an immedia e dec... eos noph ls to almost subnormal values (38 10⁶/l a... 2 weeks of treatment no lymph nodes were palpable... 2 months IgG was normal (16 g/l) and IgM lower ... The immunoglobul n band had d sappeared ... months the pat ent has no s gns of the d sease ... and IgM 1 16 g/l

Lymphocyte s ud es

Lymphocytes were solated from heparinized blood and exam ned by d rect mmunofluoresce...



F g 2 H stological ... of lymph node dem... vessel w h h gh end... surrounded by l... and many large nucle... cells (immunobla... toxyl n and eosin ...



Fig 3 Histological picture of lymph node demonstrating reticulin pattern outlining vascular proliferation Gridley s reticulin method ×95

...earlier (8) B lymphocytes were identified by staining with TRITC labelled F(ab) fragments of goat anti... Fab (Nordic Immunological Laboratories Til... The Netherlands) or by FITC labelled F(ab) frag... of an anti-CLL serum which was earlier shown to ... the B-cell specific antigen(s) (1) T lymphocytes ... identified by their receptors for sheep red blood cells ... percentage of lymphocytes with each marker was ... ined by examination of 200 cells The total number ... T-lymphocytes per liter blood was then calculated ... the total white cell count and differential count of the ... ated heparinized venous blood

... marker studies were performed before treatment ... later when there was definite clinical im... ment The results are given in Table 1 The number ... ng B lymphocytes was very low on both occa... with some tendency to increase after treatment The number of T lymphocytes was only slightly reduced A high proportion of the lymphocytes lacked all markers

DISCUSSION

The histological lymph node picture of our patient suggested the diagnosis of angioimmunoblastic lymphadenopathy Clinically the case fits well into this category except for one crucial point namely his very low B lymphocyte count This was confirmed by the concordant finding of a low number of S Ig positive lymphocytes and of lymphocytes expressing a B cell antigen defined by an antiserum against CLL lymphocytes

1 *Peripheral blood lymphocytes before (I) and after (II) treatment percentage of lymphocytes and number of cells in whole blood with surface membrane immunoglobulin (S Ig) B cell antigen or ... s for sheep red blood cells (SRBC)*

Not done

	S Ig		B cell antigen		Receptors for SRBC	
	%	×10⁶/l	%	×10⁶/l	%	×10⁶/l
I						
	0 5	9	n d	n d	57	1 069
	3 5	54	2 5	39	77 5	1 199
...ndividuals						
	1 7	249	12 5	246	80	1 593
	9 23 5	147–431	9–22	156–403	69–89 5	1 261 1 780

In almost all reported cases of AILD there has been a decrease in T cells and an increase in B cells Neiman et al (6) mean that this depends on a loss of suppressor T cells in a florid immune reaction Jones et al (3) however report 3 cases with low values of both B and T cells Our patient is presumably the first case reported with almost normal T cell values and low B cell counts In addition a high proportion of the lymphocytes lacked B and T cell marker It is noteworthy that our patient has been able to produce a high number of plasma cells in the marrow and lymphatic tissue and had high levels of IgG and IgM with hardly any circulating B cells It is also interesting that the clinical and histological picture of the abnormal immune response can be almost the same when it is correlated to a B cell deficiency instead of the more common T cell deficiency and/or B cell increase

REFERENCES

1 Berntorp E Turesson I & Zettervall O Heterologous B cells antisera may detect non Ig non HLA DR antigen Scand J Immunol 10 17 1979

2 Frizzera G Moran E & Rappaport H [illegible] immunoblastic lymphadenopathy Am J Med [illegible] 1975

3 Jones D B Castleden M Smith J L [illegible] L & Wright D H Immunopathology of [illegible] immunoblastic lymphadenopathy Br J Cancer [illegible] 1053 1978

4 Lukes R J Immunoblastic proliferations [illegible] the *Boerhaave International Course on* [illegible] Lymphomas 1979

5 Lukes R J & Tindle B J Immunoblastic [illegible] adenopathy A hyperimmune entity [illegible] Hodgkin s disease N Engl J Med 29[illegible] 1 19[illegible]

6 Neiman S Dervan P Haudenschild C & [illegible] R Angioimmunoblastic lymphadenopathy [illegible] structural and immunologic study with review of [illegible] literature Cancer 41 507 1978

7 Pattengale P K & Reichelderfer P S [illegible] of sheep red blood cell (E) rosettes with high [illegible] weight compounds Immunol Commun 4 179 [illegible]

8 Turesson I Berntorp E & Zettervall O [illegible]pression of a human B lymphocyte antigen and [illegible] membrane immunoglobulin by lymphoid cells from [illegible]tients with *lymphocytic lymphoma* multiple [illegible] and benign monoclonal gammopathy Acta Med [illegible] 206 37 1979

Acta Med Scand 208 241–242 1980

EDITORIAL

To Treat or not to Treat—Is This the Question?

people would regard it as a truism that all ...ses should be treated The only difficulty may ...nnected with the definition of the word dis... Medical history knows of disease pictures ...have lived for a limited time and then dis...ared One of the most remarkable was the so-...d status thymico-lymphaticus It was thought ...mainly children suffered from this condition ...ometimes it occurred also in adults The most ...ng symptom was an enlarged thymus gland In ...persons e g criminals who were executed or ...le who died suddenly from accidents the gland ...usually surprisingly large It was generally ...ved that people with this "stigma were prone ...come criminals or die a sudden death from ...essness! When the diagnosis was made in chil... X ray treatment of the thymus was recom...ded

...e eminent Swedish histologist and endocrinol... J Aug Hammar was able to prove that the ... of the gland was much bigger in people who ... a sudden death in contrast to those who suf...d from chronic debilitating disease Chronic ...se causes shrinking involution of the gland ... is the pathological state! The bigger gland is ...ormal His findings ended the discussion about ...teresting condition The only disease that ...ned was the fact that some of the irradiated ...ren developed thyroid carcinoma later in life ... is the classical example of the type noli me ...re the untouchable condition I think about ...eatment" of a non-existing disease may have ...hreatening consequences

...en if we are quite convinced in our present ... highly developed medical science that we do ...ommit any such terrible errors it may perhaps ...ppropriate to ransack our own conscience ... many persons with asymptomatic bacteriuria ... been unnecessarily treated with chemotherapy ...tibiotics? Some of these persons have had ...e reactions and some have become seriously ...om the treatment We live in an age when we ...ors cannot give modern potent drugs just in ...r to feel safe ourselves or know that we have not missed something It is a great responsibility to start treatment with many of our modern methods and also to abstain from treatment For psychological reasons both doctor and patient feel much happier when some treatment is instituted than if nothing is done

We are now used to find the newspapers full of descriptions and warnings about drugs and this is of course characteristic of our time It is true however that unnecessary medication or operation has been ridiculed for many centuries Moliere has given us some terrible descriptions e g in le malade imaginaire G B Shaw wrote a wonderful comedy about the doctor s dilemma and describes a fashionable surgeon who has detected a new disease He is unique in being able to make the diagnosis to remove the so-called nuciform sack and thus enjoy a lucrative practice in this field It is said that Shaw got this idea from real life A famous London surgeon was known for his treatment of the so-called Lane s kink in the abdomen that nobody else could find

The most scathing irony in a description of medical practice is to be found in Knock ou le triomphe de la medecine by Jules Romains It describes the systematic indoctrination of a small city by an unscrupulous young doctor He teaches the people to become ill and develops an enormous practice by such systematic health care The whole story is of course a blatant exaggeration but we must admit that many traits in modern medicine are similar in principle I do not want to shock anybody in particular but many of us have helped to create a feeling of ill health in persons or in groups who do not suffer from anything really serious

If I take the example renal glucosuria this is a rare disease and therefore not very important in the population at large On the other hand it may cause much trouble for the individual patient You may read even in modern textbooks that persons who have this anomaly should be carefully observed regarding real diabetes This is nonsense and is founded on some single observation that a man with

renal glucosuria developed true diabetes It would of course be strange if all renal glucosurias were immune against such a common disease as diabetes! The underlying mechanisms are entirely different even if glucosuria is the common result

I now come to my own field of experience One of the characteristic symptoms in myeloma or macroglobulinemia is the presence of a sharp peak on free electrophoresis of plasma proteins or a sharp band in electrophoresis on solid substrates Such bands have been called M-components There has been much discussion regarding the diagnostic importance of such an M component It is now clear that only the connection of this finding with other symptoms and signs allows a correct diagnosis to be made Investigations of large numbers of sera from unselected normal populations have indicated that the presence of an M-component in the large majority of instances does not indicate any serious disease It is just a biochemical anomaly like renal glucosuria

The difficulty lies in the fact that it is impossible to state with abolute certainty that this is not the very first symptom of a serious disease Many doctors may therefore be tempted to use what they would call prophylactic treatment with cytostatic drugs This is however an absurd idea for several reasons Only a very small percentage of these persons will ultimately develop myeloma or clinical macroglobulinemia The number of persons with an ever lasting benign condition is very large and it would be technically impossible to subject all such persons to the supervision that is necessary when cytostatic drugs are being used The third and most decisive argument is connected with the dangers of long term cytostatic treatment It is known that acute myelogenous leukemia develops in a small number of patients who have received long term treatment with cytostatics We may even run the risk that we kill more healthy persons by giving cytostatics—thus causing acute leukemia—than we might possibly postpone the development of myeloma This is an excellent example when therapy may be more dangerous than the "disease

There are many similar examples in medicine When the Allied Forces in World War II were exposed to the risk of yellow fever in Africa, a pr vaccine was developed The vaccine howeve cluded human serum fortuitously con ar with the virus of common hepatitis Many d are of the opinion that more healthy person from this inoculation than would have been and died with yellow fever

From my personal experience I want to qu final example that shows how treatment of symptoms in a special disease may cause the of the patient Acute porphyrics need seda their acute abdominal symptoms may temp doctors to make laparotomies in narcosis It is well known that most sedatives and drugs u general anesthesia cause severe symptoms th even lead to death The remarkable drop m tality to almost zero in this condition has bee tained by avoiding drugs that are deadly for ca of the porphyria gene Similar examples eve as dramatic constitute the modern science of macogenetics

Primum est non nocere is an old saying th to be modified many times when therapy re the old expression to expel the devil with the Beelzebub In a deadly disease such as acute kemia it seems permissible to use drugs that in themselves be deadly in order to have a to obtain some real improvement or even sa patient s life The excuse for using drugs th severe symptoms of intoxication is of course edge that there is a fair chance that they m some good in the long run

The most controversial chapter in the discu to treat or not to treat is the use of cytostatic in all patients with solid carcinomas We know some of these persons may have a few month even longer of comparative well being if n whereas cytostatic drugs usually cause seve validism during the rest of the patient s life therapeutic value is nil in a large percen patients Sometimes life is even shortened b treatment

To treat or not to treat?—This is a real qu

Jan G Waldens

BOOK REVIEWS

M d al Bullet n Chem cal Carc nogenes s vol I (I n) 1980 Sc en f c Ed tor P Brookes 104 £7 20 Published by The Brit sh Counc l 65 Davies London W1Y 2AA

mbe of the Brit h Med cal Bullet n s the fourth in s about chem cal carc nogenes s f rst started by ale Haddow in 1947 Haddow was one of the lead ng h oncology and he ed ed the earl er numbers perb way In 1958 Kennaway Haddow s predeces head of the Chester Beatty Institute gave an excel v ew of his fundamental wo k on benzpyrenes and mportance for the carcinogen c effect of cigarette

present volume also contains many chapters of t for the worker in experimental oncology It is ensac howe er that hardly more than + 10 pages roblems in human medicine As a matter of fact six e pages are devo ed to ep dem ology some pages e fascinating subject of asbestos and other f bres nnections with a s ck person may otherw se be ned cursorily e g in the d scuss on of bacterial lism and human carcinogenes s The explanat on a o dance of clinical p oblems s easy to f nd f the 19 authors only one (the stat stic an) is an l the others are PhD DSc or s m lar

This tendency for the non med cally tra ned to take over med cal nvest gation seems to me really serious Med c ne is a subject that should above all treat the problems of s ck people Knowledge about such quest ons s of course fundamental for good med cal research Two years ago I spent some very st mulating months in Bethes da USA One of my friends there—an em nent nves t gator—told me w th some malice the invest gators here are so happy because they th nk they have found a human model for a mur ne d sease Th s gives the problem in a nutshell

The volume can hardly be recommended to the cl n cian but workers in the lab will f nd excellent and interest ing presentations of some of the r problems DNA as a target of alkylat ng carcinogens DNA damage and its repair tox c ty of fungal products are some examples Ethyl n troso urea and bra n tumors in the rat is a fascinat ng story illustrated by experiments on cells in t ssue cul ture

Let us hope that the f fth number in th s mportant series will be more cl n cally oriented

Jan G Waldenstrom

...om n B ology and Med c ne Ed ted by ... Gregoriad s 363 pages $46 00 Academ c Press ...rk 1979

a ery mportant and ra her sensat onal volume It our attention to p oblems that sometimes seem to ...ters from sc ence f ction At the same t me the ...eats a cla s cal problem n med cal therapy how to ...ight target when adm nistering a drug One of the ...and most imaginative of med cal research inves... Paul Ehrlich wrote about a magic bullet that ...or hit the right target He was also the f rst to talk ...pecific side chains bind ng fore gn substances to ...surface Drug Carriers in B ology and Med c ne ...ese problems from many view po nts ...dea to attach drugs to immunoglobul n molecules ...y bind specifically to tumor cells is rather recent ...rece ed great inte est at a time when tumor ant... very much d scussed Other s milar drug carriers ...lectins that n eract w th carbohydrates in a very ...way o glycoproteins are also discussed at some ...Perhaps the most fas nating idea is connected ...fabrica on of small synthet c globules that e ther ...tive substances on the r surface or conta n such ...ces n solution The active drug may be l berated ...trategic point when transported in the blood Not ...thetic carriers of this k nd but also red blood cells ...ve su h activ ty ...vident that most inborn errors of metabol sm are

caused by a lack n some spec f c enzyme One example is the spec al type of hered tary hypogammaglobul nem a that seems to be caused by a def c ency of adenos ne deaminase Th s enzyme prevents the accumulation of adenos ne a substance that is obv ously toxic for im munocytes that produce immunoglobul n Transfus ons of normal erythrocytes have exerted a favourable influence probably through the r content of the lacking enzyme Other s m lar metabol c d sturbances may be attacked in the same way These methods of adm n strat on seem to be more p om s ng than ntravenous nject on of enzyme that is rap dly destroyed or excreted It is poss ble that the same princ ple may be used also in the treatment of Gaucher s and Fabry s d eases

Another poss ble way of attacking such problems would be to transplant some organ that contains cells producing the lacking factors Perhaps the first idea of this kind was tested by the transplantat on of normal spleens to dogs suffering from canine hemoph lia These experiments were not very successful The idea has also been followed up in human med c ne by the transplantation of a normal k dney to a pat ent w th Mb Fabry These pat ents f nally d e from k dney d sease and it is therefore ndicated with k dney transplantat on In one pat ent the procedure seemed to give prom s ng results also as regards the metabol c defect and not only by correct ng the renal shutdown Splen c transplants have also been tried n Gaucher s d sease

Even if such transplantation experiments obviously are

connected with many complications it seems as if trans plantation of cells carrying active substances and surviv ing in the recipient with continued production would be more practical Interesting experiments have been made by infusion of normal liver cells into animals suffering from metabolic diseases of the liver Survival of the trans plant is of course the problem

Already in 1936 autotransplantation of parathyroid glands was performed after total thyroidectomy Such examples have been performed on a large scale and there is no question about the fact that a take occurs also func tionally

The most exciting type of experiment with this technique has been performed by pancreatic surgeons It seems as if also allographs may survive if islet cells are injected into the portal vein The liver is obviously an excellent soil for the culture of islet cells Such experi ments work surprisingly well in rats In man, the [illegible] techniques of islet cell transplantation have been [illegible] diabetics who were on immunosuppression be[illegible] previous kidney transplantation Perhaps the most [illegible] ising situation could be autotransplantation of [illegible] prepared from the surgically removed organ [illegible] with chronic pancreatitis and severe pain The [illegible] is still very limited but the idea is promising

Japanese authors have been much interested in [illegible] ing artificial membranes that may be biodegrad[illegible] release their content of active substances It is [illegible] sible that such plans are only the products of [illegible] speculation On the other hand it seems [illegible] follow such developments and the contributors [illegible] volume are eminently competent to describe the [illegible] day state of affairs

Jan G Walde[illegible]

Atlas of Human Hemopoietic Development By E Kele men W Calvo and T M Fliedner 266 pages US$202 40 DM 368 — Springer Verlag Berlin Heidel berg and New York 1979

As stated by Marcel Bessis in the foreword the present book makes us realise once more that morphology is the science of structure and shape and that its aim is not to collect pictures but to understand them The authors have used the 22 first pages for an introductory text part about the extra-embryonic and fetal hemopoiesis Here the data based on studies of 190 human embryos and fe tuses are summarized in nine tables and five figure curves which show the quantitative change in the cellular com position of the hemopoietic organs during embryonic and fetal development

The most impressive part of this book is certainly not the text and tables but the photographs They are of the highest quality both in black and white and in colour An artist would envy the picture of circulating primitive erythroblasts in the 7–8 week old embryo The use of vari ous magnifications and also electron microscopic photo graphs enhances the impression of the dynamic pro- gression of events Each photographic plate is explained on the opposite page Unfortunately however [illegible] explanatory symbols are very rarely used on the [illegible] graphs From the artistic point of view this [illegible] advantage but for the reader it is a tiring proce[illegible] the right cell among 20–30 when indicated [illegible] located at the center left at lower third" of the [illegible]

The wonderful photographs are also poorly [illegible] the introductory text part Although this part is [illegible] in the same way as the plates i e diffuse [illegible] intravascular hemopoietic cells and organ bound [illegible] poiesis referral to the plates is only rarely [illegible] referral at all is made to the electron microscopic [illegible] The dynamics of events at the subcellular level [illegible] fore poorly clarified to the reader

These limitations should not blur the view that [illegible] is probably unsurpassed for those who want to [illegible] morphology of hemopoiesis during embryonic [illegible] development It is a book for the specialists the [illegible] and the institutions (hematologic morphologic [illegible] and cytologic) The price will probably limit [illegible] spread

Gosta Gahrton H ddinge S[illegible]

Acta Med Scand 208 245–256 1980

Smoking Habits in the Glostrup Population of Men and Women, Born in 1914

Implications for Health Evaluated from Ten Year Mortality Incidence of Cardiovascular Manifestations and Pulmonary Function 1964–1974

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RACT Of a total population of 514 men and omen born in 1914, from seven municipalities nhagen County 87 % were examined in 1964 74 Smoking habits (inhalation kind of tobac mount duration of smoking and changes over ade) have been described in this age-specific, al population The health implications were med Tobacco consumption was in this popula the most important risk factor for overall mor cardiovascular manifestations, peripheral ar disease decline in pulmonary function and ions of ulcer The results are consistent with prospective epidemiological studies The rela sk of death, of fatal and nonfatal cardiovascu anifestations and of decline in pulmonary func ncreased gradually with the amount of tobacco ed Inhalation roughly doubled the risk The risk for pipe/cheroot smokers was less than or cigarette smokers Ex smokers reduced their about 50 % The risk associated with smoking independent of other factors The excess risk utable to smoking was as great in women as in but the community problem of smoking related ses was most pronounced in men, among whom ing habits are more widespread and morbidity her The results from the 1914 population study st that almost one third of all deaths and heart ks in middle-aged Danes might be avoided, if year-olds would have given up smoking

ords bronchitis cardiovascular diseases mortality ective studies respiratory function tests smoking

Med Scand 208 245 1980

ing is a significant probably causal risk factor tal mortality and cardiopulmonary diseases in Western industrialized countries as shown in al prospective epidemiological surveys (26) 1914 population study gives a picture of the ten year mortality and incidence of smoking related diseases in an age specific general population of men and women according to duration of smoking inhalation amount and kind of tobacco smoked

STUDY POPULATION AND METHODS

Population

The 1914 population in Glostrup comprises the 514 men and 461 women (the total population of 50-year-olds) who in 1964 were living in seven municipalities around the Copenhagen County Hospital in Glostrup 802 were examined at entry (14) In 1974 the 890 survivors were reinvited and 666 participated in the reexamination

Procedure

A description of the selection and representativity of the population and the design of the study are given elsewhere (14 28) The surveys of 50- and 60-year-olds included questionnaires fasting blood and urine specimens resting and exercise ECGs pulmonary function tests X rays and a social-psychiatric section When available WHO standardized questionnaires were used (27) Questions about smoking habits are Danish translations of the questionnaire about smoking habits (27) Only one interviewer posed the questions to all participants in a single survey (L Hagerup in 1964 M Schroll in 1974) The answers were transformed into variables describing different aspects of the smoking habits 1) Tobacco consumption (38) 1 cigarette – 1 g 1 cigarillo=3 g 1 cigar=5 g never smokers ex smokers smokers of 1–14 15–24 or more than 25 g/day 2) Tobacco consumption (g/day × no of years of smoking) Lifetime tobacco consumption (kg) 3) Smoking habits never smokers ex smokers cigarette smokers smokers of pipe cigars and cigarillos mixed consump-

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Abbreviations CVD=cardiovascular disease AMI=acute myocardial infarction FEV_1=forced expiratory volume in 1 sec

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Table I *S nok ng l abits in tl e 1914 pop latio 1 in Glostri p at tl e age of 50 i 1964*

	Males		Females		Total	
	N	%	*N*	%	*N*	%
Present smokers	340	78	217	59	557	69
Inhalers	247	57	115	31	362	45
Never smokers	42	10	128	35	170	21
Ex smokers	54	12	21	6	75	9
Consumpt on per day (g)						
1 14	136	31	151	41	287	36
15 24	125	29	52	14	177	22
>25	76	17	11	3	87	11
Unknown	3	1	3	1	6	1

tion 4) Inhalation nonsmokers and non inhaling smokers inhalers 5) Ex smokers for more than 10 years (qu tted smok ng before 1964 and d d not resume) for less than 10 years (qu tted smoking between 1964 and 1974 but d d not smoke for one year before the survey)

The mpl cat ons of smok ng for health have been evaluated by relat ng hab ts to ten year mortal ty ten year ncidence of fatal and nonfatal card ovascular d seases (CVD) and pulmonary funct on

Copies of death cert f cates of part c pants who had d ed between 50 and 60 years of age were obta ned from the Nat onal Health Serv ce The causes of death were veri f ed from d scharge records of hosp tal cases Autopsy was performed n 68% of the 85 deaths Causes of death were reg stered accord ng to the internat onal class f ca t on (ICI) (37) Informat on about card ovascular man fes tat ons (CVD) at the age of 50–60 were derived from death cert f cates d scharge records the Copenhagen Heart Reg ster and the survey in 1974 The ten year ncidence of CVD in ludes fatal and nonfa al ca es of acute myo infarct on (AMI) (ICI 410) o her heart d eases is mat c (ICI 390–394) schaem a heart fail re arrhy (ICI 411–4 9)) cerebrovascular attacks (ICI 430– peripheral arterial d sease when verif ed by arteri (ICI 440) Fatal cases verif ed by au opsy and other cases n whom two of three cl n al criteria typical serial ECG and enzyme changes) po n ed to the diag were regarded as cases of myocard al infarct on. St attacks w th focal neurolog c symptoms of [illegible] vascular orig n and of more than 24 hou s dura regarded as cerebrovascular manifesta ons F one woman had had a CVD before 1964 They subgroup in the mul ivariate CVD ana yses Among the BMRC quest onna e on bronch s and pulm funct on tests have been described thoroughly (forced exp ratory volume n 1 sec (FEV) was mea by a Godart exp rograph The change n pulmonary t on between the ages of 50 and 60 years (the s l ne connect ng 50 and 60 year values) wa d fferences n FEV at en ry by d s on w th the value

$$\frac{FEV_{60} \quad FEV_{50}}{FEV_{60}+FEV_{50}}$$

Smok ng hab ts have been related to othe variables const tut onal factors soc al ba kground tors l v ng hab ts and health nd ca ors (9

The informat on was checked for m ss ng and ble values and analyzed n the SCIBAS sys em (un variate analyses nonparametric sta s cal tests used χ^2 W lcoxon Mann Wh tney Kru kal W the Spearman rank correlat on tes To e alua e the smok ng ndependent of other r k fac ors m analyses were appl ed W th t me between the survey n 1964 and death or f rst card o ascu ar t on as end po nt the Cox regress on model 30 was

Table II *S nok ng l ab ts c t tl e c ge of 60 n 1974 in tl e 1914 pop ilat on n Glostr p*

	Never smokers	Ex smokers	Consumpt on per day (g) 1 14	15 24	>25	Inhalers
Men (n=360)						
Never smokers	38					
Ex smokers		79				31
C garette smokers			36	48	11	85
P pe and c gar smokers			55	40	22	44
M xed consumpt on			12	11	8	25
Total	38	79	103	99	41	185
Women (n=306)						
Never smokers	120					
Ex smokers		26				
C garette smokers			80	20	3	6
Pipe and c gar smokers			41	11	4	16
M xed consumpt on				1		
Total	120	26	121	32	7	83

III *Changes in smoking habits between the ages of 50 and 60 in 670 men and women examined in* ...nd 1974

	Age 60				
	Never smokers	Ex smokers	1–14 g/d	15–24 g/d	>25 g/d
...(n 335)					
...smokers	76	7	2	0	0
...okers	5	33	7	2	1
...mption per day (g)					
...4	4	18	52	30	3
...4	1	12	27	44	14
	1	7	7	16	21
...(n 335)					
...smokers	97	2	5	1	0
...okers	6	9	2	1	0
...mption per day (g)					
...4	11	12	78	10	2
...4	1	2	19	15	3
	0	0	3	3	3

...ulmonary function at the age of 60 as end point analyses were applied (36). In the multivariate ...division of the coefficient with its standard de... gives a test observate (the U-obs value) 1.96 ...a statistical significance on the 5% level and ...the 1% level. The strength of the association ...n smoking habits at entry and ten year mortality/ ...ity is expressed as the "relative risk"

...ce (mortality) among smokers
...or category of smokers)
———————————————
...ce (mortality) in nonsmokers

The "attributable or excess risk" is: Incidence among smokers−incidence among nonsmokers.

Relating the attributable risk to the distribution of smoking habits gives the "population attributable risk". Attributable risk × prevalence of a certain category in the population.

RESULTS

Smoking habits

Table I shows the smoking habits in the 1914 population at entry in 1964 at the age of 50. The sex

IV *Ten year mortality related to smoking habits at the age of 50 at entry*

	N	Deaths	Absolute risk per 1000		Relative risk	Attributable risk per 1000	Population attributable risk N	%
...smokers	47	2	48 (6–167)					
...okers	54	4	74 (21–179)					
...mption per day (g)				82	1.00	–		
...14	136	13	96 (50–154)					
...24	125	15	120 (66–184)		1.46	38	4.8	9.4
	76	17	224 (136–334)		2.73	142	10.8	21.2
	433	51	117 (94–167)					30.6
...n								
...smokers	128	4	32 (8–77)					
...okers	21	1	48 (1–238)					
...mption per day (g)				43	1.00	–		
...14	151	8	53 (23–103)					
...24	52	4	77 (21–185)		1.79	34	1.8	9.5
...5	11	2	182 (23–518)		4.23	139	1.5	7.9
	363	19	52 (29–73)					17.4

Table V *Ten year mortality related to inhalation at the age of 50 at entry*

	N	Deaths	Absolute risk per 1 000	Relative risk	Attributable risk	Population attributable risk	
						A	C
Men							
Noninhalers	196	13	66 (35–109)	1 00	–	–	
Inhalers	240	38	158 (113–207)	2 39	92	??	43
Total	436	51	117 (94–162)				43
Women							
Noninhalers	250	11	44 (22–78)	1 00	–		
Inhalers	116	8	69 (29 128)	1 57	25	2 9	15
Total	366	19	52 (29 73)				15

difference was pronounced 35% of females and 10% of males had never smoked 70% of the female smokers had a moderate consumption compared to 40% of the male smokers 48% of female smokers and 76% of male smokers were inhalers

Table II gives the corresponding information about smoking habits in 1974 at the age of 60 There was a tendency towards a reduction of con sumption as the percentage of ex smokers had doubled thereby diminishing the other smoking categories Table II combines information on amount with the type of tobacco smoked In this elderly Danish population a strikingly high propor tion (48%) of the men smoked a pipe cigars or cheroots The distribution of pipe/cheroot smokers over moderate medium and high tobacco consump tion was 47 34 and 19% which does not much from the distribution of cigarette smokers roughly 10 20 and more than 20 a day 35 [illegible] 15% No women but 25% of the men were smokers (12 g/day on average) Only 1% of women and 5% of the men smoked cigars [illegible] Cheroots were preferred by 25% of the men [illegible] and 18% of the women (6/day) At 60 years [illegible] 35% of the men and 34% of the women smoked cigarettes (22 and 11/day respectively) Of cigarette smoking men 87% were inhalers [illegible] pared to 38% of the pipe/cheroot smokers [illegible] ratio was the same among women

Table III gives the individual changes in smoking habits between the ages of 50 and 60 but it points to some methodological problems [illegible]

Table VI *Ten year mortality related to kind of tobacco smoked at the age of 50 at entry*

	N	Deaths	Absolute risk per 1 000		Relative risk	Attributable risk per 1 000	Population attributable risk	
							A	C
Men								
Never smokers	42	2	48 (6–162)	63	1 00		–	
Ex smokers	54	4	74 (21–179)					
Pipe and cigar smokers	152	14	92 (52–15?)		1 46	29	4 4	8 6
Cigarette smokers	188	31	165 (114–224)		2 6?	10?	19 ?	37 6
								46 2
Total	436	51	117 (94–162)					
Women								
Never smokers	128	4	31 (8–77)	34	1 00	–	–	
Ex smokers	21	1	48 (1 238)					
Cigarillos	67	3	45 9 125)		1 32	11	0 7	3 7
Cigarettes	150	11	73 (77–128)		2 15	39	5 9	31 1
								34 8
Total	366	19	52 (29–73)					

II *Cardiovascular manifestations related to smoking habits at the age of 50 at entry*

	N	CVD	Absolute risk per 1000		Relative risk	Attributable risk per 1000	Population attributable risk N	%	p
mokers	4?	?	48 (6–16?)	91	1 00	–			0 0?
kers	54	7	130 (54–?49)						
ption per day (g)									
	136	12	88 (45–145)						
	1??	13	104 (69–179)		1 14	13	1 6	3 3	
	76	15	197 (115–305)		2 16	108	8 ?	16 7	
	43?	49	112 (9? 156)					20 0	
mokers	1?8	0	0 (0 0–?8)	?7	1 00				n s
kers	21	0	0 (0 0–161)						
ption per day (g)									
	151	8	53 (4? 136)						
	5?	6	115 (44–?34)		4 26	88 0	4 6	25 6	
	11	4	364 (109–69?)		13 48	337 0	3 7	?0 6	
	363	18	50 (?7 70)					46 2	

the information takes the form of answers to ...rd zed interviews it depends on a judgement ...t surprising to find a transition between adja... roups but 18 smokers at the age of 50 ought ...d be described as never smokers at the age ...

...el e men and 9 women classified as ex smok... the age of 50 took up smoking again before ...e of 60 Another 37 men and 14 women gave ...noking Once established smoking habits ...ed only a little making it possible to estimate ...nd vidual s life consumption this averaged ... in men and 75 kg in women The pronounced ...ffe ence was due to the higher prevalence of nonsmokers among the women and a later start Most of the men started to smoke around the age of 20 25% already between 10 and 14 Half of the women started after the age of 45 only 25% before the Second World War and only 10% before the age of 20

Implications for Health

Ten year mortality (all causes) among men and women according to smoking habits at the age of 50 (Table IV)

The total ten year mortality was 11 7% among men and 5 2% among women Only 69% of the 1914

VIII *Ten year incidence of cardiovascular manifestations in relation to inhalation at the age ... at entry*

	N	CVD	Absolute risk per 1000	Relative risk	Attributable risk per 1000	Population attributable risk N	%	p
halers	196	17	87 (50–133)	1 00				0 00?
rs	240	32	133 (89–176)	1 53	16	11 0	2?4	
	436	49	112 (9? 156)				2?4	
n								
halers	250	6	32 (9–5?)	1 00	–			n s
rs	116	10	86 (41 148)	2 69	54	6 3	34 8	
	366	18	49 (27 70)				34 8	

Table IX *Ten year incidence of cardiovascular manifestations in relation to kind of tobacco s[illegible] age of 50 at entry*

	N	CVD	Absolute risk per 1 000	Relative risk	Attributable risk per 1 000	Population-attributable [illegible] N	%
Men							
Never smokers	42	2	48 (6–162) } 94	1 00	–	–	
Ex smokers	54	7	130 (54–249) }				
Pipe and cigar smokers	152	16	105 (62–168)	1 12	11	1 7	1
Cigarettes	188	24	128 (83–182)	1 36	34	6 4	13
Total	436	49	112 (92–156)				16
Women							
Never smokers	128	0	0 (0–28)	–	–	–	
Ex smokers	21	0	0 (0–161)	–	–	–	
Cigarillos	67	5	75 (25–166)	?	75	5 0	77
Cigarettes	150	13	87 (47–144)	?	87	13 0	72
Total	366	18	49 (27–70)				100

population were smokers but 84% of the deaths occurred among smokers a significant overmortality ($p<0.03$) The relative risk increased steadily with increasing amounts of tobacco smoked per day by a factor that was not smaller for women With small numbers in each class confidence limits of absolute risk overlapped and relative risk has been calculated in relation to a combined group of non and moderate smokers Attributable risk measures here the excess mortality of >15 g tobacco per day among smokers Population attributable risk gives a theoretical maximum value for the percentage of ten year mortality in the population under observation that would have been avoided if the 50-year olds had stopped smoking (15 of 51 deaths in men)

Table V shows the same calculations for inhalation a habit which significantly doubled the mortality among men, even though the group of noninhalers included quite a large num[illegible] ers who consumed a considerable amo[illegible] co per day

Table VI shows that the risk for [illegible] smokers was greater than that for ex sm[illegible] the risk for cigarette smokers doubled [illegible]

Causes of death were mainly ma[illegible] plasms (35%) and cardiovascular dise[illegible] No significant overmortality from ma[illegible] plasms among smokers in this populatio[illegible] in ten years

Ten year incidence of fatal and nonfatal [illegible] cular manifestations in men and wome[illegible] to smoking habits at the age of 50

Table VII shows that 87% of the ca[illegible] manifestations occurred in the 69% of [illegible] tion who smoked at the age of 50 (p[illegible] relative risk of smoking was especia[illegible]

Table X *Lifetime tobacco consumption related to morning cough/phlegm at the age of 60 population in Glostrup*

	Men (N = 360) Consumption (kg)	S D	Women (N = 306) Consumption (kg)	S D	Total (N = 666) Consumption (kg)	S D	P
No symptoms	206	194	59	100	133	171	<
Symptoms	295	226	123	109	233	209	
All	238	211	75	106	163	189	

XI *Pulmonary f ct on and fall n p ln onary f nct on at tl e age of 50–60 i relat on to s ok g he age of 60 n the 1914 pop lat on i i Glostr p*

	FEV (l)				FEV (50 60) / FEV (50+60) 00			
	360 men***		306 women*		360 men* *		306 women	
	$\bar{X}$	S D	$\bar{X}$	S D	$\bar{X}$	S D	$\bar{X}$	S D
nokers	3 03	0 5	2 10	0 4	9 9	9 9	7 7	13 5
.ers before 1964	2 86	0 5	2 04	0 4	10 3	?0 ?	4 4	19 5
. rs afte 1964	2 74	0 6	2 05	0 5	15 4	16 9	8 7	7 6
;tion pe day (g)								
	2 80	0 5	1 94	0 5	10 ?	1? 3	14 2	16 4
	2 58	0 6	1 93	0 4	16 4	15 3	1? 1	11 5
	2 74	0 6	1 99	0 3	8 9	15 5	9 9	8 4
gar smokers	?84	0 5	2 03	0 4	11 0	13 7	11 7	13 7

n rank correla on *R* value between FEV and kg tobacco/l fe was 0 16
$p<0\ 001$

on y female smokers had heart attacks at e decade As the ncidence of CVD was ch among male ex smokers there was no excess risk for male smokers

: VIII shows that inhalat on was of impor the increased nc dence of CVD among s Only 5 of 31 myocard al infarctions among men occurred in non nhalers ($p<0\ 004$)

Tab e IX it w ll be seen that p pe/cheroot s had a lower nc dence than cigarette smok n when the amount of tobacco smoked in the ups was almost the same (Table III)

g hab s and o l er card o asc lar i a ons

e alence and nc dence of ang na pectoris ng to the Rose quest onna re were not re lated to smoking hab ts n th s populat on at entry Neither was there any strong or cons stent relat on sh p between ECG chances and smok ng hab ts Smok ng was a h ghly s gn f cant r k factor for peripheral arteriosclerot c d sea e In a separate re port (31) it is shown that the correlat on b t een l fet me tobacco consumpt on and the ndex of ankle/arm blood pressure was *R* 0 ??

P ılmonary sympto s a d f nct on n rel t n to sn ok ng l ab ts

Table X shows the h ghly sign f cant associat on between morn ng cough/phlegm and l fetime tobac co consumpt on (age 60) From Table XI t w ll be seen that pulmonary funct on (FEV) and change in FEV with age (or over t me) were more favourable among nonsmokers than smokers An nterest ng

XII *Mul aria e analys s (Cox regress on model) of tl e relat onsl p bet een t me of deatl (o p exam na on n 1974) and six basel ne var ables meas red at tl e age of 50 n 1964*
ab es were a ailable n 763 persons 63 d ed before the age of 60

: ariables	Coeff c ents	S D	U-obs	Level of s gn f cance
g hab ts				
nokers				
ump ion per day (g)	0 6161	0 6961	0 8850	n s
-14				
4	0 7690	0 5666	1 3571	n s
5	1 1549	0 5832	1 9803	$p<0\ 05$
	1 6555	0 60 9	2 7458	$p<0\ 01$
l heart ra e	0 0240	0 0091	2 6270	$p<0\ 01$
ucose o h gh nsu in levels	−0 2553	0 4057	0 6 92	n s
lucose and h gh insul n levels	1 0137	0 4848	2 0909	$p<0\ 05$
nia	0 8370	0 2731	3 0645	$p<0\ 01$
ex	0 0760	0 0223	−3 4079	$p<0\ 01$
	1 1553	0 3533	3 2704	$p<0\ 01$

Table XIII *Multivariate analysis (Cox regression model) of the relationship between time of card... lar manifestation (or follow up examination in 1974) and seven baseline variables measured at the... 50 in 1964*

All variables were available in 790 persons after exclusion of CVD cases before the age of 50 57 cardiovascular manifestation before the age of 60

Baseline variables	Coefficients	S D	U-obs	Level of significance
Diastolic BP (mmHg)	0 0327	0 0106	3 0955	$p<0\ 0001$
Smoking habits				$p<0\ 0001$
Ex smokers	2 7216	1 0327	2 1903	
Consumption per day (g)				
1–14	2 6191	1 0327	2 5362	
15–24	3 0888	1 0426	2 9625	
>25	3 3994	1 0590	3 2100	
Ischaemia (age 50)	0 7227	0 2969	2 4343	$p<0\ 05$
Physical activity at work				$p<0\ 05$
Moderate active	−0 6722	0 3158	−2 1287	
Active	−1 0321	0 3963	−2 6042	
Heavy work	−0 6171	0 5753	−1 0726	
No of rooms at home	0 2091	0 1099	1 9023	$p<0\ 05$
Relative weight				
(% of Natvig s tables)	0 0112	0 0075	1 4827	n s
Male sex	0 2927	0 3125	0 9367	n s

difference was observed in $FEV_{1\%}$ in ex smokers for more and less than ten years respectively The FEV_1 of pipe/cheroot smokers was intermediate

The relationship between smoking and other variables—the independent risk of smoking

Smoking habits were significantly related to other variables measured at the ages of 50 and 60 years (29) As these relations might modify the association between smoking habits and death/CVD/FEV_1 they have been included in multivariate analyses of the independent risk of smoking They were ... status number of rooms in apartment ed... marital status consumption of alcohol co... tea leisure activity and max aerobic powe... pressure resting heart rate overweight d... haematocrit and pulmonary function an... chitis

Table XII gives the relationship to t... of different smoking groups controlled for ... tioned baseline variables (Cox regression ... Only the six variables of significant impor... the risk factor model are given in the t...

Table XIV *Logistic analysis (Duncan-Walker) of the relationship between low FEV_1/height (the lo... of the distribution) and six variables measured at the age of 60 and univariate associated wi...*

	Coefficients	S D	U-obs	Level of signif...
Constant	−0 90001	0 7001	−1 2836	–
Male sex	−2 2607	0 2415	−9 3611	$p<0\ 00001$
Cough in the morning	1 1210	0 2413	4 6461	$p<0\ 001$
Ex smokers/nonsmokers	0 2091	0 3443	0 6072	n s
Cigarette smokers/nonsmokers	0 7133	0 2614	2 7282	$p<0\ 01$
Pipe and cheroot/nonsmokers	0 1571	0 2859	0 5496	n s
Mixed consumption/nonsmokers	0 2670	0 5928	0 4503	n s
Social status class				
5/1–4	0 4867	0 6510	0 7476	n s
6/1–4	1 2466	0 5642	2 2097	$p<0\ 05$
7/1–4	0 9815	0 5678	1 7284	n s
8/1–4	1 2335	0 5768	2 1386	$p<0\ 05$
No of rooms in apartment	−0 1117	0 0763	−1 4649	n s
Average no of drinks/day	−0 0079	0 0498	−0 1593	n s

cent for pipe/cheroot smokers was similar to or ex smokers and moderate smokers (0 81)

ble XIII gives accordingly the risk factors for n year incidence of CVD The coefficients n are higher for daily use of tobacco than for ther variable indicating the independent im nce of smoking as a cardiovascular risk factor coefficient for pipe/cheroot smokers was 9 in a similar analysis where only amount of co smoked was exchanged with the kind of co smoked as baseline Other confounding bles related to smoking habits at entry did not independently to time of CVD from baseline mation that is there was no statistically sig nt difference between their coefficients and and they are therefore not given in the table

ble XIV shows that pulmonary function at the f 60 was directly related to sex symptoms of hitis smoking habits and social status ac ng to Svalastogas classification (28) The risk low FEV_1/height was more pronounced in ts due to body build in coughers in cigarette ers and in people with a low social status few rooms in the apartment Alcohol intake nrelated

DISCUSSION

s cohort of Danes born in 1914 nine out of ten out only two out of three women had been rs The women *had also started to smoke* n life than the men The mean tobacco con ion was moderate A considerable part of the rs were pipe/cheroot smokers Two thirds of okers were inhalers

1914 population is an age specific total ation from a defined geographic area It com 1 7% of the 1914 birth cohort in Denmark At lection in 1964 it was representative of the 1914 cohort in sex social and occupational bution (14) Ten year mortality and incidence VD were also the same as in the 1914 birth t (28)

the persons originally invited 13% never ap d at the health examinations Non partici for whom baseline data were obtained at e of 60 differed from participants examined in smoking habits (fewer men were non rs) pulmonary symptoms (more men had a ng cough) and pulmonary function (lower values in men as well as women) ($p<0.05$) lations between smoking and tobacco-related diseases derived from examination of the partici pants will probably not be less pronounced in the non participants

The age specificity (all participants born in 1914) facilitated the interpretation of results because the incidence of diseases in the heart and lungs is age specific and to a different degree in the two sexes Smoking habits also differ between birth cohorts due to differences in individual influences over time (secularization) The smoking habits described in the 1914 population accordingly represent smoking habits of Danes in that year

Studies on tobacco consumption of Danes have been published before (3 16 17 21 22 23) The figures in Table III in the present paper are almost identical with those concerning 50–64 year old Danes in a Gallup market analysis in 1975 (21) The influence of the neighbouring capital Copenhagen might be mirrored in a slightly higher frequency (52%) of female smokers in Glostrup than in the country as a whole (44%)

The smoking habits in the 1914 population seem quite unchanged since they were established as seen when compared with the Danish National Morbidity Survey in 1952–54 (16 17 23) i e when the 1914 population was 40 years old Their smoking habits in 1974 (Table III) are very similar to those of 30–39 year olds in the morbidity survey but differ from 50–59 year-olds at that time Stated age of par ticipants *when starting to smoke was also in agree* ment with our findings most men born 1911–14 started to smoke before the Second World War compared to only one third of the women The 1914 population differs from younger generations of Danes (21 22) The tendency during the century has gone towards fewer smokers more female smokers and more inhaling cigarette smokers

Differences in smoking habits were also ob served when the Glostrup population was com pared with age comparable foreign populations (e g Swedes Americans) Only 56% of the 50-year old men from the 1913 population in Gothen burg were smokers (35) though as many as in Glos trup were cigarette smokers (47%) since only 9% smoked pipe/cigars The proportion of male smok ers in the USA is the same as in Denmark but individual consumption is higher and the majority are cigarette smokers More Danish than American women of this age were smokers and their use of cheroots is a national characteristic (21 33) The differences regarding the year of bi d na

tionality must be kept in mind when the results from the multivariate analyses of smoking and related diseases are compared between populations

Overmortality among middle aged male smokers is known from several prospective studies (9 10 11 26 35) The results of the ten year mortality study in Glostrup are consistent with these findings showing that Danish male smokers are at increased risk like smokers of other nationalities The figures in Table VI do suggest a similar relative risk in female smokers although the numbers here were not statistically significant This is important for the individual female smoker The community problem was less pronounced in females as only 3 deaths in 366 women could be attributed to overmortality among smoking women compared to 15 excess deaths in 436 men

The proportion of pipe/cheroot smokers was larger than in most studies making it possible to estimate the absolute risk for male non cigarette smokers This was only a little higher than that for never smokers and ex smokers The relative risk compared to never smokers was 1 9 In the 1913 population in Gothenburg it was higher 2 8 and similar to that of cigarette smokers (35) Differences in inhalation habits might explain the discrepancy

The strong association (high relative risk) of smoking with mortality makes it probable that smoking is a causal risk factor (26) This possibility was strengthened by the gradually increasing risk with increasing amount of tobacco smoked and the independency of other risk factors The effect of smoking on mortality was even increased when allowance was made for the influence of overweight and hypertension The hypothesis that the association between smoking and death was secondary to some underlying characteristic (4) was tested indirectly with the same result as in some other studies (9 10) None of the confounding variables were independently associated with ten year mortality making the hypothesis improbable This implies that the harmful effect of smoking is due to the smoke The psycho social risk factors of becoming a smoker will be the subject of another analysis of the 1914 investigation

The mortality of the ex smokers was lower than that of smokers As some of the registered ex smokers may have taken up smoking again after the baseline survey (Table III) and as some had been ex smokers for only a short time the possibility remains that persistent ex smokers may have the same mortality after some years as never [illegible] (11 15)

The effect of intervention against smok[illegible] last and important argument in the d[illegible] causality—has not been examined in the 19[illegible] lation in Glostrup as the population was [illegible] touched between the surveys the purpos[illegible] descriptive and analytic Monofactor interv[illegible] against smoking in controlled clinical trials has [illegible] effected successfully after myocardial inf[illegible] (18) Primary prevention trials are under way [illegible] average 25% of the participants remain ex[illegible] ers a year after the intervention The effect on mortality of this has not yet been evaluated [illegible]

Smoking is known to be the most [illegible] causal factor for the increase in malignant [illegible] plasms Although this could not be demon[illegible] the present population study substantial evi[illegible] has been obtained from other Danish studies [illegible] the 1914 population smoking was related to [illegible] symptoms (12) ten year incidence of CVD [illegible] peripheral arteriosclerotic disease (31) pu[illegible] function (1) and changes in pulmonary f[illegible] This underlines the importance for health a[illegible] this very common habit However smok[illegible] of specificity has been used as an argume[illegible] the causality of smoking It has then been [illegible] that impaired pulmonary function is a com[illegible] nominator for the diversity multiplicity and [illegible] tive non specificity of the effect of smoking [illegible] morning cough age 50 and $FEV_{1.0}$ were si[illegible] risk factors for death of all causes in the 1914 [illegible] lation (1) Smoking was probably partly a ri[illegible] tor for death through the effect on pu[illegible] symptoms and function The coefficients for [illegible] ing were reduced though still significant [illegible] FEV_1 was introduced in the analysis of ind[illegible] risk factors of time to death Pulmonary f[illegible] was best in never smokers gradually de[illegible] with increasing exposure Smokers of more [illegible] one pack a day were a small group p[illegible] selected by resistance to the harmful e[illegible] smoking on the respiratory system and s[illegible] up the habit Ex smokers benefitted from g[illegible] smoking (8 19) and more so as time [illegible] Ex smokers 1964–73 may have quitted smok[illegible] cause of symptoms due to it

A strong relationship between cigarette [illegible] and FEV_1 (corrected for body build by d[illegible] height) persisted when allowance was [illegible] possible confounding variables such as [illegible]

alcohol A social factor coexisted with the [smoki]ng factor This might be explained by the [predo]minance of childhood infections in lower so[cial cla]sses Few rooms in the apartment may fur[ther i]ncrease the effect of smoke on pulmonary [functio]n (34)

[Pulm]onary function at baseline did not feature as [a card]iovascular risk factor (28) Other properties of [tobacco] are probably responsible for the triggering [effect] on heart attacks Platelet adhesiveness [increased] carboxyhaemoglobin levels and increased [myoca]rdial irritability have been mentioned as [pathog]enic effects (2 11) In the 1914 population [atheros]clerosis was already manifest at entry To[bacco] smoking was the most important risk factor [for CV]D probably due to this triggering effect [These] findings are highly consistent with results [from o]ther population studies the risk gradually [increas]ed with the amount of tobacco smoked (15 [...] 38) Ex smokers reduced their CVD risk by [stoppi]ng the smoking habit (15) The absolute risk [of ...]/cheroot smokers was similar to that of [...smo]kers and moderate smokers as known from [res]ults published by others (38) The relative [risk of] CVD in women was as impressive as in men [...]

[Smok]ing is theoretically a risk factor amenable to [...] The results of the 1914 population survey [sugges]t that almost one third of all deaths and heart [...] in middle aged Danes might be avoided if [not le]st one in ten but all 50-year olds became [non-smo]kers before age 60 The question is how this [knowle]dge can reach the individual smoker and [caus]e a change in smoking habits sufficient to [reduce] the morbidity in smoking related diseases [...]rd CVD mortality are still increasing in mid[dle age]d Danish men compared to the USA where [they a]re now decreasing (due to a change in smok[ing ha]bits?) (33) The smoking habits of younger [genera]tions of Danes do not promise a decrease in [smokin]g-related diseases when these individuals [reach] middle age The problem will probably in[crease] among women in particular In Denmark [preve]ntion against smoking and help to individual [smoke]rs who wish to quit smoking are practically [nonex]istent The authorities have as yet been re[luctant] to do anything but impose tobacco taxes (7) [Prev]entive effort supporting smokers who wish [to sto]p smoking and investigations of initiating fac[tors i]n children and youngsters would seem to be [well f]ounded

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REFERENCES

1. Agner E Christensen F Hagerup L Hansen P F & Schroll M Respiratory symptoms and pulmonary function in 50 and 60 year olds Eur J Resp Dis To be published
2. Ball K & Turner R Smoking and the heart The basis for action Lancet 2 822 1974
3. Bonnevie P Befolkningens rygevaner Ugeskr Laeger 126 1433 1964
4. Cederlof R Friberg L & Lundman T The interactions of smoking environment and heredity and their implications for disease etiology Acta Med Scand (Suppl) 612 1977
5. Clemmensen J Statistical studies in the aetiology of malignant neoplasms Acta Pathol Microbiol Scand (Suppl) 247 1974
6. Cohen B H Hypothesis Is pulmonary dysfunction the common denominator for the multiple effects of cigarette smoking? Lancet 2 1024 1975
7. Egsmose T Vort tobaksproblem Ugeskr Laeger 138 2508 1976
8. Fletcher C Peto R Tinker C & Speizer F E The natural history of chronic bronchitis and emphysema Oxford University Press New York 1977
9. Friedman G D Dales L D & Ury H K Mortality in middle aged smokers and non smokers N Engl J Med 300 213 1979
10. Goldbourt U & Medalie J H Characteristics of smokers non smokers and ex smokers among 10000 adult males in Israel Am J Epidemiol 105 75 1977
11. Gordon T Kannel W B McGee D & Dawber Th R Death and coronary attacks in men after giving up cigarette smoking Lancet 2 1345 1974
12. Hagerup L Geismar P & Rahbek I Ulcer symptoms in a population of 50 year olds from the Glostrup investigation in 1964–65 Ugeskr Laeger 133 1022 1971
13. Hagerup L & Larsen M Tobacco smoking and respiratory symptoms in a Danish population Ugeskr Laeger 133 1302 1971
14. Hagerup L M Coronary heart disease risk factors in men and women From the population study in Glostrup Denmark Acta Med Scand (Suppl) 557 1974
15. Hammond E C Smoking in relation to diseases other than cancer Total death rates In The Second World Conference on Smoking and Health (ed R G Richardson) pp 24–34 Pitman Medical & Scientific Publishing Co London 1971
16. Hamtoft H & Lindhart M Tobacco consumption in Denmark I Dan Med Bull 2 213 1955
17. — Tobacco consumption in Denmark II Dan Med Bull 3 188 1956

18 Hansen A T Schnohr P & Rose G Ischemic heart disease The strategy of postponement F A D L /Year Book Medical Publishers Copenhagen 1977

19 McCarthy D S Craig D B & Cherniack R M Effect of modification of the smoking habit on lung function Am Rev Respir Dis 114 103 1976

20 Mortensen L S & Larsen M E A database system for scientific purposes In Recent developments in statistics (ed J R Barra) pp 705–707 North Holland Publishing Co Amsterdam 1977

21 Nielsen P E & Krarup N B Tobaksforbruget i Danmark 1920–1975 Ugeskr Laeger 138 2511 1976

22 Nielsen P E Krarup N B Astrup J Gyntelberg F & Lisse O Ændring i danskernes rygevaner 1958–1976 Ugeskr Laeger 140 2528 1978

23 Norgaard A Tobacco consumption in Denmark III Dan Med Bull 6 54 1959

24 Rasmussen F V Borchsenius L Holstein B & Solvsteen P Lung function and long term exposure to cement dust Scand J Respir Dis 58 252 1977

25 Reid D D McCartney P Hamilton P J S Rose G Jarrett R J & Keen H Smoking and other risk factors for coronary heart disease in British civil servants Lancet 2 979 1976

26 Report of the Royal College of Physicians Smoking and health now Pitman Medical & Scientific Publishing Co London 1971

27 Rose G A & Blackburn H Cardiovascular survey methods WHO Geneva 1968

28 Schroll M & Hagerup L M Risk factors of *myocardial infarction and death in men aged 50 at* entry A ten year prospective study from the Glostrup population studies Dan Med Bull 24 252 1977

29 Schroll M A ten year prospective study 1964–1974 of cardiovascular risk factors in men and women from the Glostrup population born in 1914 Dan Med [illegible] To be published

30 Schroll M & Larsen S A ten-year pro[illegible] *study of cardiovascular* risk factors in [illegible] women from the Glostrup population born [illegible] Multivariate analyses Dan Med Bull To be [illegible]lished

31 Schroll M & Munck O Estimation of [illegible] arteriosclerotic disease by ankle blood [illegible] measurements in a population study of 60 [illegible] men and women J Chron Dis To be published

32 Slone D Shapiro S Rosenberg L Kau[illegible] W Hertz S C Rossi A C Stolley [illegible] Miettinen O S Relation of cigarette [illegible] *myocardial infarction in young women* N Engl [illegible] 298 1273 1978

33 Stamler J Introduction to risk factors in co[illegible] artery disease In Cardiology series vol 1 [illegible] Fig 18 (ed H D McIntosh) Medical Com[illegible]tions Northfield Illinois 1978

34 *The Pooling Project Research Group* Relation[illegible] blood pressure serum cholesterol smoking [illegible] lative weight and ECG abnormalities to inci[illegible] major coronary events Final report of the [illegible] Project J Chron Dis 31 201 1978

35 Tibblin G & Wilhelmsen L Rok[illegible] riskfaktor Lakartidningen 68 687 1971

36 Walker S H & Duncan D B Estimat[illegible] probability of an event as a function of several [illegible]pendent variables Biometrika 54 167 196[illegible]

37 WHO Klassifikation af sygdomme [illegible] *1969 Sundhedsstyrelsen* Copenhagen 19[illegible]

38 Wilhelmsen L Wedel H & Tibblin G [illegible]tivariate analysis of risk factors for coronary disease Circulation 48 950 1973

Acta Med Scand 208 257 ?63 1980

Coronary Ischaemıa and Occlusıon ın Gıant Cell (Temporal) Arterıtıs

J W Paulley

Fro n Ips I Hosp tals Ips c/ Engl nd

RACT Reports of coronary artery involve in giant cell (temporal) arteritis–polymyalgia atica (GC(T)A PMR) together with other arteries aris ng from the aorta have been ous over the past 40 years but on this the li t card ac l terature has been virtually silent rt cle summarises that evidence and records dd t onal patients from a large group of cases oth GC(T)A PMR and ischaemic heart d sease observed since a previous report in 1960 The istor es illustrate the benefit from corticoste- and the hazards of non diagnosis and pre e cessation of such treatment It seems that patients with arteritic IHD (and claudicat on) being identified before or after death Pos- reasons for this oversight by cl nicians and log ts are offered and suggestions are made egard to po nts in h story taking and important al s gns wh ch may help to alert the cl nician is autopsy evidence from Malmo Sweden that e alence of GC(T)A PMR is much higher than sent suspected on cl n cal grounds

ord ang na pectoris myocard al nfarct on g ant mporal arteri s coronary arterit s
Med Scand 208 257 1980

act that coronary arteries are as l kely to be ed by giant cell (temporal) arterit s (GC(T)A) o he large arteries aris ng from the aorta is n but ra ely vo ced Much of the evidence of m eda ed a prev ous commun cation (4?) n t was suggested inter al a that the cardiac ort c presentat ons of the disorder were l kely more common than was recognised It may be to cal nterest that th s observat on based on shed h stopa hology and supported by cl n cal nce was unacceptable to an assessor at the but on appeal the art cle was publ shed was also suggested on cl nical ev dence (39 4?) GC(T)A and polymyalg a rheumatica (PMR) phases of the same d sorder Th s too provoked controversy (? 43 49) but the hypothes s was later confirmed by positive b opsy of apparently normal temporal arteries in PMR (1) and of large arteries of the h p and shoulder g rdles (?0) All important stud es s nce have been n accord w th these find ngs

In 1960 Hughes and I rote D agnost c fa lure in GC(T)A is due to many d verse presentat ons some of wh ch are l ttle kno n and to a cont nued acceptance of a too r g d prof le of the d ease The passage of ?0 years has seen greatly impro ed recognition of the tempor l and polymyalg c phases w th the result that much pa n and bl ndne s have been prevented However other man fe tat ons of GC(T)A cont nue to go unsuspected ı ndete ted and untreated in part cular arterit c ischaem hea t d sease (IHD) claud cat on and aortic aneur m The l terature and personal experience also suggest that the gastro ntest nal (7 16 41 4?) nd psych at ric presentat ons (8 16 4? 50) are be ng over looked as well

Regard ng arter t c IHD w th h ch e are ma n ly concerned here the spec al st card olog cal l t erature w th one exception (15) has rema ned s lent whereas reports in the l terature of gener l med cine and pathology have been numerous e er since Gilmore s report in 1941 (14) of the nvolve ment of the aorta and its major branches by GC(T)A It must therefore be assumed that car d olog sts are e ther see ng the d sorder but not d agnos ng it or are diagnos ng it but not report ng

PATIENTS FOR THE PRESENT STUDY

The writer s exper ence of pa ents w h IHD and h s tolog cally proven GC(T)A and of other pa ents n whom

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Abb e at ons GC(T)A g ant cell (temporal) arterit s PMR polymyalg a rheumat ca IHD schaem c heart d sease MI myocard al nfarct on

biopsy was not sought or obtained has been extensive since the previous report in 1960 when 9 out of 76 patients had IHD Of over 100 cases seen over 20 years 9 have been selected to illustrate various aspects of presentation responses to treatment and hazards of relapse when corticosteroids are reduced prematurely either through over-optimism or inadequate supervision Three cases with positive arterial biopsies are reported in detail six are described more briefly In the latter six patients diagnosis was made on clinical grounds supported by laboratory findings in only two of these was arterial biopsy performed it was positive

THREE CASE HISTORIES

Case I

A married woman of 62 on 6 3 75 presented with angina of effort 2 months after 50 m and also claudication She had had terrible buttock pain in Dec 1978 Only after close questioning did she admit left jaw pain for 9 days On examination left carotid artery tender and facial arteries thick and non pulsatile Bruit over left carotid and left brachial artery bruit to the elbow ESR 126 mm Hb 10 3 g/100 ml Increased α and γ globulin Facial artery biopsy positive for arteritis vessel thrombosed but giant cells absent ECG ischaemic S T depression in V3 V4 and a Q3 Treatment with prednisone 10 mg t i d was started on 6 3 75 with dramatic improvement the patient was able to do stairs and 250 m up hill after only 5 days of treatment Discharged 21 3 75 on prednisone 5 mg t i d ECG 21 379 had reverted to normal ESR 21 mm

The patient has been observed for 4½ years until time of writing On 4 8 75 a mild relapse of angina pectoris ESR at that time 35 mm Prednisone increased to 12 5 mg In Aug 1976 she said she was so fit my husband cannot keep up with me Left brachial bruit was still present but on 8 4 79 it could not be heard She then had occasional angina of effort up hill in cold weather but no claudication Resting ECG normal

The patient initially denied mourning but then admitted ock and grief at the loss of two close friends six months (confirmed by husband) and much later casually entioned that her mother had committed a particularly nasty suicide having escaped from the mental hospital where she had been admitted after finding the patient s sister dead in the lavatory The patient had been unable to mourn either at the time

Case II

A man of 69 referred with angina pectoris and claudication of 3 months duration on 9 10 78 by a doctor who had successfully treated temporal arteritis 15 months previously Prednisone had been tailed off after 6 months Examination facial arteries thickened bilateral brachial and iliac artery bruits right fundus ischaemic ESR 76 mm α_2 globulin + resting ECG normal Temporal artery biopsy internal elastic lamina destroyed intimal proliferation lumen virtually occluded wholly compatible with arteritis 14 months previously Treatment with prednisone 30 mg/day was started In 3 days he reported that he had resumed work as a gardener to a large factory without angina or claudication Two months later still present ESR 8 mm/h Prednisone gradually [illegible] to 10 mg/day

The patient did not attend follow-up on [illegible] of snow but on 15 5 79 he said that [illegible] after a long walk and that he had reduced his [illegible] dose to 5 mg/day 3 weeks before and some [illegible] to take it ESR 95 mm ECG showed S-T depression [illegible] and V5 On prednisone 5 mg t i d his [illegible] remitted and on 20 8 79 he was "very well" ES[illegible] arm bruits still present but iliac bruits absent

Mourning first denied by the patient was [illegible] vealed by his wife His youngest daughter had left [illegible] live with a married man six months before [illegible] poral arteritis He would have nothing to do [illegible] but his wife could not bear to lose her you[illegible] this led to a rift between patient and wife and [illegible] loss of her as well a replication of the loss of [illegible] mother when he was a child Brief psychotherapy [illegible] his mourning and brought the spouses together [illegible]

Case III

A married woman of 73 Angina of eff[illegible] rheumatologist 2 years previously "Tra[illegible] When seen on 19 1 78 she was breathless [illegible] after 50 m She had had jaw pain chewing for [illegible] had lost 12 kg Left facial artery thick and [illegible] lateral brachial bruits to elbow and over femor[illegible] to the knee ESR 22 mm increase in α Facial [illegible] opsy destruction of internal elastic lam[illegible] broelastic intimal thickening and a minute [illegible] cytic foci in media and few giant cells The [illegible] ally disappeared in 10 days on prednisone [illegible] gained her lost weight

Mourning was anticipated her husband [illegible] very ill with his prostate She had feared he [illegible] and that she would lose him as she had lost [illegible] much earlier Her feelings for both were [illegible]

BRIEF NOTES ON SIX CASES

Case IV

A single woman of 67 had temporal arteritis [illegible] biopsy in 1974 Corticosteroids were reduced [illegible] sion of ESR insufficient She relapsed with angina [illegible] and claudication in 1977 with an ESR of 58 mm [illegible] over right carotid and left subclavian arteries [illegible] increase in corticosteroids improved exercise [illegible] from 50 to 150 m however her ESR remained [illegible] head pains recurred during reactivation of [illegible] mourning reaction ESR 93 mm Unfortunately [illegible] priate action was not taken and the patient was [illegible] dead three months later with the presumptive [illegible] myocardial infarction (MI) or more remotely [illegible] section

Case V

A married woman of 69 pre[illegible] in 197[illegible] with [illegible] gardening or walking 50 m PMR responded to [illegible] in 1972 when ESR was 125 mm She now [illegible] brachial bruits ESR was 53 mm Left bundle [illegible]

Autopsy histology positive for GC(T)A in coronary arteries

xonary C = carotid T temporal A = aorta R radial Re renal Sc subclavian Br = brachial Bas = Op ophthalmic CI ciliary Vert vertebral S mes = superior mesenteric

s)	Year	Clinical presentation	Extent of arteritic involvement demonstrated
(1	1935	Temporal acute blindness	Co and Ca
al (10	1945	Polymyalgia head pain blindness confusion	T Co ARF S mes Re
theim (13)	1951	Head pains MI	A Co Iacs Sc
(45)	1951	Cerebral thrombosis rheumatism	A Br Ca Bas Co ovarian
all et al (24)	1954	Polymyalgia acute blindness	T A Ca Co
n & Ab bol (34)	1955	Head pain blindness fever MI	T Op Co circle of W I s
& Bonnin (3)	1956	Head pains PUO acute blindness MI	T A Ca Co lingual Op
m (11)	1959	Head pains fever acute blindness MI	T Ca Vert Op CI
& Hoyt (46)	1960	Head pains acute blindness MI	T A Iacs Ca Co Op CI
n & Be an (23)	1967	Polymyalgia head pains blindness MI	Op Ca Co
2	1968	Aortic aneurysm rupture	Lingual Ca A Co
et al. (18)	1968	Polymyalgia acute blindness	T Co Ca A Sc S mes
(3)	1973	-	Co in 3 of 6 cases of GC(T)A PMR examined
al (31)	1975	Polymyalgia abdominal pain aortic aneurysm cardiac arrest	A Co and all main aortic branches examined

angina pectoris responded to restoration of pred 15 mg/day At last follow up on 31 8 78 ESR 8 angina left brachial bruit still present Mourning prior to onset and unresolved through course of

ed woman of 75 admitted with proven MI in 1968 y was hampered by fever and pericarditis for 3 ESR 9 mm raised α She denied previous tism headache or head pains but later admitted "Where?" In my head" She had misheard her diagnosis of arteritis but had responded to pred However when he emigrated she stopped taking drug as she did not want to trouble or face his or Reintroduction of prednisone led to immediate y Mourning prominent at outset and in relapses

II

w of 55 who never really got over the loss of her d but had coped with the support of a cousin "more ster" A few months after the shock of losing the m 197 she suffered severe head pains and tender r 7 months In 1975 she was referred with severe l wo months duration Her aorta was tender right rtery thick and barely pulsating Blood was drawn R and electrophoresis and her doctor was advised to initiate treatment with prednisone He replied patient had had a major coronary on the evening 75 (the day after she was seen) and died later that efore prednisone could be started (ESR 71 mm and ed α) Pathological mourning had been intensified tis just prior to onset of PMR

III

ried woman of 69 was referred in 1977 with angina g her to stop every 50 m The onset occurred 2 months after an alienation from a favourite daughter whose marriage and departure to a distant city she had been unable to accept Her abdominal aorta was palpable and tender with a bruit ECG was ischaemic and ESR 34 mm Five days after a trial with prednisone she was *able to walk further and her hands and feet felt warmer* Six months later she was able to do ¾ mile without angina At follow-up in 1979 she remained well on a small dose of prednisone and had an ESR of 18 mm

Case IV

A widow of 76 who had declined in health since nursing her husband in his terminal illness the previous summer was admitted with left heart failure and confusion in April 1966 Temporal arteries were thick and tender biopsy positive ESR 54 mm α + Through her confusion she told of severe head pains before her husband's death and thereafter exhaustion muddle headedness and angina Treatment with prednisone was started 14 days after admission and *brought about a dramatic improvement in her* confusion and refractory cardiac failure as well as ECG and ESR On postal follow up her daughter said she had remained well for 12 months but had become confused again when prednisone had been reduced to 4 mg day When admitted later to another department her prednisone was promptly stopped despite an ESR of 83 mm and the patient died shortly after a series of strokes

DISCUSSION

Table I summarises reports of histologically proven GC(T)A in the coronary arteries and other arteries also affected and chief clinical presentations

The following references firstly relate to reports of patients with histologically proven GC(T)A

PMR who died of MI within 6 months of diagnosis and who were not autopsied (9 30 47) and secondly to reports of myocarditis or death from myocardial failure in patients with GC(T)A (16 29 37 38) Lastly there are reports of patients surviving with histologically proven GC(T)A–PMR with angina pectoris or associated MI (6 33 35 42 48)

At present the percentage of patients in whom GC(T)A–PMR coronary arteritis affects the quality or expectation of life is unknown Personal experience suggests that the answer may be frequently especially in partly treated or inadequately controlled cases just as dissecting aneurysm of the aorta has been shown to be a complication to be reckoned with for the same reason by Klein et al (31) They recorded aortic rupture in 3 out of 34 patients with clinical evidence of arteritis of the aorta and main branches

Other unknowns are the real incidence of GC(T)A–PMR in the general population and in how many cases the disease continues to smoulder after initial treatment and how many of these die of MI or myocardial insufficiency In a disorder with such a broad spectrum of presentations (42) some even now rarely recognised such as aortic regurgitation (25 42) and affecting especially the stoical and bereaved (40 42) it is not surprising that figures of incidence and prevalence derived from clinical data (17 21 27 28 36 44) fall far short of the most substantial autopsy evidence to date Östberg (37) reporting from Malmo found GC(T)A in 1 4% of 560 consecutive adult autopsies in which she examined a transverse section of the aorta 5 cm above the aortic valve In a subsequent series of 889 autopsies in which an additional section of aorta from the level of the diaphragm and also sections of the temporal artery were examined the finding of giant cell arteritis rose to 1 7% Östberg concluded that this is a minimum figure and since the lesions are patchy there is a considerable chance that a few small specimens will miss the arteritic changes Her comprehensive studies confirm the importance of intimal changes presenting as pearly cushion-like areas and in the later stages progressing to fibrosis of the intima and adventitia with shrinkage of the lumen The classical changes in GC(T)A in the media require no emphasis but Östberg reiterates the warning that giant cells are "not a consistent finding" except during the phase of elastin degradation and adds The name of giant cell arteritis therefore seems but little appropriate but is probably too well es[illegible] changed As to how often arteritis [illegible] patients presenting with IHD the[illegible] data to help Östberg found the coron[illegible] involved in 3 out of 6 cases known [illegible] GC(T)A–PMR previously but clearly [illegible] work still remains to be done This pres[illegible] require a study comparable to Östberg's [illegible]secutive series of autopsies after MI and [illegible] be difficult because of the patchy [illegible] arteritis and the frequency of assoc[illegible] (37 42) some of which perhaps develop[illegible] sponse to the arteritic insult Such a ca[illegible] relapse associated with mourn[illegible] mourning was observed closely over [illegible] towards the end her aorta was almost [illegible]cified

Allowing for such difficulties car[illegible] others will ask why in view of Östberg's f[illegible] few more cases have not been reported [illegible] autopsy One can only make sugges[illegible] may be significant that most of the [illegible] showing coronary involvement were [illegible] most of those patients were blind following [illegible] temporal arteritis and most had not [illegible] ticosteroids or corticotrophin which [illegible] prevented blindness or if they did [illegible] probably for insufficient time to su[illegible] tis Allowing 2 3 years lag between [illegible] lication this fits closely to the general [illegible] these remedies which in the UK for [illegible] steroids was about 1957 Personal e[illegible] the literature since 1960 show that [illegible] arteritic phase is now usually [illegible] treated which is why arteritic blindness [illegible] less common It seems that what [illegible] cians and also presumably patholog[illegible] tending to see are smouldering [illegible] poorly monitored cases in which the [illegible] main branches including the coron[illegible] have become gradually involved (31) ([illegible] classic example despite close su[illegible] tient reduced his prednisone dose [illegible] dramatic relief of his angina and [illegible] to relapse temporarily with an ESR of [illegible] supervision been less close the ou[illegible] have been MI)

So unless the histopathologist is [illegible] clinicians when a patient with MI [illegible] autopsy has had or is thought [illegible] GC(T)A PMR he is unlikely to look for [illegible]

esence of obvious atheroma and thrombi to this hospital clinicians often do not know a patient admitted with MI has been treated IR-GC(T)A because the general practitioner ot think to mention it being unaware that ry disease claudication and aortic dissection tential sequelae

iagnostic pointers

ng the better histological evidence there are eatures which should alert the clinician that a presenting with MI or angina pectoris may nderlying GC(T)A (*a*) A history of head n the preceding year or two facial neuralgia shoulder polymyalgia or claudication needs phasis However it is less well known that ent is likely to be in pathological mourning y figure or surrogate and the surrogate may ouse child friend or pet This observation ade 20 years ago recurs in case after case the rule rather than an exception (40 42) and n validated by independent observers of un d videotaped interviews of 12 patients with A PMR (*b*) The mourning reaction is ab- lly protracted because of ambivalent feelings s the key figure(s) Grief is usually concealed ed until the patients are asked whether any they have lost are much in their thoughts If y is X is never out of my thoughts accom by a quivering lip or break in voice a point added to the index of suspicion (*c*) Malaise ll persisting beyond expectation and delaying ry together with a raised ESR persisting d 3 weeks after MI and for which no other can be found often accompanied by raised ulin (*d*) In the event of any of (*a*) (*b*) (*c*) positive a most careful examination should de for thickening and/or tenderness of tem facial occipital carotid arteries and for over much longer lengths of vessel than with ma notably to the elbow over the brachial s and often from the iliacs to the knee over r s canal (18) The abdominal aorta itself may der (41) and aortic valve incompetence may leveloped (25 42) If (*d*) is positive the clini nay decide to ask for a biopsy of facial or ral artery bearing in mind that it may still be ve even in the presence of active GC(T)A ng the aorta coronaries and other branches s may be reluctant to submit such sick people o such a relatively mild procedure as facial/ temporal artery biopsy especially if other evidence has been enough to decide on a trial of cortico steroids in any case

The arteriographic studies of Klein et al (31) and Hamrin (17) clearly show the reason for the exten sive bruits in GC(T)A–PMR Whether improved coronary arteriography will help to differentiate ar teritic areas from atheroma remains to be seen

Diagnostic pitfalls

Not only may temporal and facial artery biopsies be negative in GC(T)A–PM (26 37 42) especially if giant cells are regarded as essential to diagnosis but in perhaps 3–5% of cases the ESR may also be repeatedly normal (6 16 35 42)

Since Bottiger and Svedberg s report (5) it is un fortunate that some geriatricians have been teach ing that a raised ESR is a normal finding in the elderly This doctrine is dangerous and it would be wise to regard it as non proven until more clinical evidence is available than provided in the above study My experience supported by Eckerstrom (12) is that elderly people have a normal ESR un less there is cause for it to be raised such as infec tion neoplasm myeloma silent large peptic ulcers subacute bacterial endocarditis rheumatoid ar thritis SLE Paget s disease and last but not least GC(T)A

Mourning and immunological response

GC(T)A–PMR is now thought by many to be an immunological disorder and Bartrop et al (4) showed that thymic mediated immunity was re duced during mourning This may explain why grief and mourning sometimes even in anticipation of the loss of a key figure are so relevant in this disorder (42 47) Because these patients have diffi culty in showing emotion some tend to endure their symptoms along with their grief until they are very ill and even dead (cases VII and IX are examples)

Indeed the physical disability coming on top of grief not infrequently leads to attempted suicide Cases of GC(T)A–PMR coming to diagnosis may only represent the tip of an iceberg of undetected disease in the elderly

CONCLUSION

It seems likely that many patients with arteritic IHD are not receiving the help they should and the same applies to arteritic claudicants The object of this

article is to pose the question whether it is better to accept the evidence we have which is substantial but imperfect and try to identify more cases of GC(T)A affecting the aorta and great vessels including the coronary arteries and treat them during life or to adopt a more scientific stance and wait for the results of more definitive autopsy studies

Cases I–III are examples of what can be done for severe angina pectoris and/or claudication when due to GC(T)A Temporal/facial artery biopsy was positive in each but head pain and polymyalgia were minimal in cases I and II at the time of the onset of angina pectoris and claudication but had occurred 15 months previously in case II

Cases IV VI VII IX are examples of the cardiac price likely to be paid for not diagnosing and treating PMR–GC(T)A soon enough or to monitor and control reactivity in a diagnosed case

The following diagnostic traps need to be stressed (*a*) Normal biopsy does not exclude the possibility of GC(T)A (*b*) Intimal proliferation without giant cells may predominate over the more commonly recognised changes (*c*) Arteritic lesions are patchy (*d*) ESR may be normal in a few cases (*e*) Severe anaemia can also cause the characteristic arterial bruits

REFERENCES

1 Alestig K & Barr J Giant cell arteritis—A biopsy study of polymyalgia rheumatica etc Lancet 1 1228 1963

2 Bagratuni L Polymyalgia rheumatica Lancet 2 1255 1961

3 Barnard W G Tuberculous arteritis J Pathol Bact 40 433 1935

4 Bartrop R W Luckhurst E Lazarus L Kiloh L G & Penny R Depressed lymphocyte function after bereavement Lancet 1 834 1977

5 Bottiger L E & Svedberg G Normal erythrocyte sedimentation rate and age Br Med J 2 85 1967

6 Bruk M J Articular and vascular manifestations of polymyalgia rheumatica Ann Rheum Dis 26 103 1967

7 Clarke Stevens J Kavanaugh J & McIlrath D C Temporal arteritis a case with abdominal arteritis presenting as a malignancy Minn Med 53 623 1970

8 Cockran J W Fox J H & Kelly M P Reversible mental symptoms in temporal arteritis J Nerv Ment Dis 166 446 1978

9 Cohen H & Harrison C V Temporal arteritis A report of three cases J Clin Pathol 1 212 1948

10 Cooke W T Cloake P C P Govan A D T & Colbeck J C Temporal arteritis A generalised vascular disorder Q J Med 15 47 1946

11 Crompton M R The renal cha[illegible] (giant cell) arteritis Brain 8[illegible] 377 19[illegible]

12 Eckerström S Sedimentation reaction [illegible] persons Nord Med 41 471 1949

13 Frangenheim H Zur Frage der Riesenz[illegible] Zentralbl Allg Pathol 88 81 1951

14 Gilmore J R Giant cell arteritis J Pathol [illegible] 263 1941

15 Hall G H Giant cell arteritis—an [illegible] Am Heart J 85 835 1973

16 Hamilton C R Shelley W M & T[illegible] Giant cell arteritis including temporal arte[illegible] polymyalgia rheumatica. Medicine (Balt[illegible] 1971

17 Hamrin B Polymyalgia arteritica. Acta Med (Suppl) 533 1–131 1972

18 Hamrin B Jonsson N & Hellsten S [illegible]gia arteritica further clinical and histopath[illegible] studies with a report of six autopsy cases Ann [illegible] Dis 27 397 1968

19 Hamrin B Jonsson N & Landberg T [illegible] polymyalgia rheumatica Lancet 1 397 19[illegible]

20 — Involvement of large vessels in p[illegible] rheumatica Lancet 1 1193 1965

21 Hansen W A Ferguson R H Holley [illegible] Kurland L T Temporal arteritis in [illegible] Minn 1951–61 Mayo Clin Proc 46 49[illegible] 197[illegible]

22 Harris M Dissecting aneurysm of the a[illegible] giant cell arteritis Br Heart J 30 840 19[illegible]

23 Harrison M J G & Bevan A T Early [illegible] of temporal arteritis Lancet 2 638 1967

24 Heptinstall R H Porter K A & Barkley [illegible] cell (temporal) arteritis J Pathol Bact 6[illegible]

25 How J & Strachan R W Aortic reg[illegible] a manifestation of giant cell arteritis B[illegible] 40 1052 1978

26 Hughes G R V Connective tissue disease [illegible] pp 225–234 Blackwell Oxford 1979

27 Huston K A Hunder G G Lie J T [illegible] R H & Elveback L R A 25 year e[illegible] clinical and pathologic study Ann Intern M[illegible] 1978

28 Jonesson F Cullen J R & Elton R A [illegible] arteritis a 14 year epidemiological cl[illegible] nostic study Scott Med J 24 111 1979

29 Kennedy L J Giant cell arteritis with [illegible] myocarditis Calif Med 115 84 1971

30 Kilbourne E D & Wolff H G Cran[illegible] critical evaluation with report of a case A[illegible] Med 24 1 1946

31 Klein R G Hunder G G Stanson [illegible] Sheps S G Large artery involvement [illegible] (temporal) arteritis Ann Intern Med 83 [illegible]

32 Lander H & Bonnin J M Giant cel[illegible] report of a case with autopsy J Pathol Ba[illegible] 1956

33 Molldrem N D & Olin R Polymyalgia [illegible] poral and coronary arteritis Minn Med [illegible]

34 Morrison A N & Abitbol M Granulom[illegible]teritis with myocardial infarction Ann [illegible] 42 691 1955

35 Mowat A G & Hazelman B L [illegible]

umatica with particular reference to arterial dis
e J Rheumatol 1 190 1974
menthaler M Giant cell arteritis (cranial arteritis)
ymyalgia rheumatica J Neurol 218 219 1978
berg G Morphological changes in the large ar
es in polymyalgia arteritica Acta Pathol Microbiol
nd (Suppl) 237 1–59 1973
ner H P & Michael I E Giant cell myocarditis
multiple organ involvement Arch Intern Med
444 1965
lley J W Anarthritic rheumatoid disease Lan
2 9–6 1956
Mortality among widowers Br Med J 2 53 1969
lley J W & Daley M P Gastro-intestinal man
tations of giant cell arteritis with aortic tender
s Biol Gastroenterol (Paris) 2 431 C 1972
lley J W & Hughes J P Giant cell arteritis or
ritis of the aged Br Med J 2 1562 1960

43 — Polymyalgia rheumatica Lancet 1 50 1962
44 Rhodes D J Giant cell arteritis in general practice J R Coll Gen Pract 26 337 1976
45 Ritama V Temporal arteritis Ann Med Intern Fenn 40 63 1951
46 Spencer W H & Hoyt W F A fatal case of giant cell (temporal or cranial) arteritis with ocular involvement Arch Ophthalmol 64 862 1960
47 Sproul E E A case of temporal arteritis NY State J Med 42 345 1942
48 Strachan R W How J & Bewsher P D Masked giant cell arteritis Lancet 1 194 1980
49 Todd J W Polymyalgia rheumatica Lancet 2 1111 1961
50 Vereker R The psychiatric aspects of temporal arteritis J Ment Sci 98 280 1952

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Zinc Balance before and during Treatment with Bendroflumethiazide

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[illegible]RACT The present study gives full balance [illegible] of zinc in two healthy individuals before and [illegible] treatment with chlorthalidone Positive zinc [illegible]ts were noted in both subjects without [illegible] During chlorthalidone treatment the bal[illegible] changed in a negative direction Thus the [illegible] or slightly increased serum zinc values which [illegible]een observed during diuretic treatment in spite [illegible]reased urinary losses of zinc cannot be [illegible]ed by increased zinc absorption Depletion of [illegible] tissues seems likely

[illegible]rds zinc balance chlorthalidone
[illegible]ed Scand 208 265 1980

[illegible]ed urinary excretion of zinc has been found [illegible] therapy with hydrochlorothiazide (2) and [illegible]halidone (6 7) Furosemide and bumetanide [illegible] raise the urinary zinc concentration However with regard to the large urine volumes pro[illegible] during such medication the amount of zinc [illegible] urine is augmented (5 10) On the other [illegible] serum zinc values in patients on diuretics are [illegible]d or even slightly raised (2 9) There are at [illegible] two possibilities to explain this circumstance [illegible] intestinal absorption of zinc might be raised [illegible] thiazide therapy or tissues may be depleted

[illegible] aim of this study was to elucidate this ques[illegible] by investigating the zinc balance in two healthy [illegible]as before and during thiazide therapy and also [illegible] thiazide therapy with zinc supplementation

SUBJECTS AND METHODS

[illegible]ealthy female technical assistants 29 and 32 years [illegible]ere subjected to the study They were kept on a [illegible] diet prepared in the metabolic ward and their [illegible] and urine were collected for 8 metabolic balance [illegible]s of 5 days The conventional carmine labelling [illegible]que was applied to separate the periods (3) The loss of zinc in urine and faeces during each balance period was determined on aliquots of urine and homogenates of faeces with the aid of atomic absorption (Varian Techtron Model 1100) The intake of zinc was determined by analysis of homogenates of duplicates of the daily menu The diet of subject A was calculated to contain 101 g protein 94 g fat and 248 g carbohydrate Corresponding values for the diet of subject B were 81 93 and 235 g

The zinc balance studies in subjects A and B were performed in the following way Periods I and II no medication Periods III and IV 5 mg bendroflumethiazide (Salures®) and 1 5 g potassium chloride daily Period V same as periods III and IV plus 7 5 mg Zn^{++} as a chloride solution twice a day Period VI 10 mg bendroflume thiazide 1 5 g potassium chloride and 7.5 mg Zn as a chloride solution twice a day Periods VII and VIII Same as period VI but the Zn supplementation was re placed by 50 mg Mg^{+} as a chloride solution

RESULTS

Table I presents the balance data of both subjects Without any medication (periods I and II) the zinc balances were positive in both The Zn intake was 14 mg in subject A and 12 5 mg in subject B 69% appeared in faeces in subject A and 70% in subject B during periods I and II A correction of the bal ances was made with regard to calculated losses of Zn by skin The loss of zinc by skin (sweat and desquamation) is estimated to be 2 8 mg daily ac cording to recently published data (4)

During thiazide therapy without Zn supplementa tion (periods III and IV) the urinary zinc excretion increased by 29% in subject A and by 55% in sub-ject B compared to their urinary excretion during periods I and II The faecal excretion during periods III and IV was 82% in subject A and 73% in subject B The corrected mean Zn balances during periods III and IV were negative in subject A and about zero in subject B During thiazide therapy with Zn supplementation the Zn balances were strongly positive in both subjects The urinary excretion of Zn during Zn supplementation rose

Table I *Zinc balance (mg/24 h)*

Period	Treatment	Daily intake	Excretion		Balance	Com-bined
			Faecal	Urinary		
Subject A						
I	None	14 0	10 4	0 25	+3 35	
II		14 0	8 4	0 22	+5 38	
Mean for I and II		14 0	9 4	0 24	+4 36	[illegible]
III	5 mg bendroflumethiazide +	14 2	12 4	0 32	+1 48	
IV	1 5 g KCL	14 2	10 9	0 29	+3 01	
Mean for III and IV		14 2	11 7	0 31	+2 19	[illegible]
V	5 mg bendroflumethiazide + 1 5 g KCL + 15 mg Zn	27 4	23 6	0 28	+3 52	
VI	10 mg bendroflumethiazide + 1.5 g KCL + 15 mg Zn⁺⁺	30 1	20 5	0 30	+9 3	
Mean for V and VI		28 8	22 0	0 29	+6 51	[illegible]
VII	10 mg bendroflumethiazide +	14 8	15 1	0 36	−0 66	
VIII	1.5 g KCL + 50 mg Mg⁺	14 9	11 7	0 41	+2 79	
Mean for VII and VIII		14 9	13 4	0 39	+1 11	[illegible]
Subject B						
I	None	12 5	8 3	0 41	+3 79	
II		12 5	9 0	0 46	+3 04	
Mean for I and II		12 5	8 6	0 44	+3 46	[illegible]
III		12 6	8 7	0 63	+3.27	
IV		12 6	9 7	0 73	+2 17	
Mean for III and IV		12 6	9 2	0 68	+2 72	[illegible]
V		27 1	19 3	0 71	+7 09	
VI		27 1	20 7	0 76	+5 64	
Mean for V and VI		27 1	20 0	0 74	+6 36	[illegible]
VII		12 4	13 1	0 65	−1 35	
VIII		13 8	14 5	0 60	−1 30	
Mean for VII and VIII		13 1	13 8	0 63	−1 33	[illegible]

only slightly in subject B and not at all in subject A The percentage excreted by faeces was about the same as during periods III and IV When Zn supplementation was replaced by Mg supplementation the Zn balances were strongly negative in both subjects and the urinary Zn excretion remained at about the same level The mean amount excreted in faeces during periods VII and VIII exceeded the intake in subject B and amounted to 90% in subject A

DISCUSSION

It has been suggested that therapy with thiazides and other diuretics may cause deficiency not only of potassium and magnesium but also of zinc (1 9)

Raised urinary losses of potassium and [illegible] potassium during medication with thiazides [illegible] furosemide has been well known for a long time [illegible] potassium supplementation is usually given [illegible] urinary losses of zinc have been found [illegible] therapy with chlorthalidone (6 7 10 [illegible] chlorothiazide (2 10) bendroflumethiazide [illegible] furosemide (5 10) bumetanide and [illegible] (10) The increased losses persisted [illegible] month s treatment with hydrochlorothiazide [illegible] after 6 months treatment with chlorthalidone [illegible] The serum zinc levels however did not [illegible] therapy (2 8 9) On the contrary in a group of [illegible] patients treated with different diuretics for [illegible] than six months the serum zinc level [illegible] higher than in 96 apparently healthy [illegible]

as explained by the effect of diuretics on olume The explanation of normal or high Zn levels in spite of increased losses in urine diuretic therapy may be either that zinc is wn from tissues causing an intracellular zinc cy or that zinc absorption is augmented in ay The present study clearly shows that sorpt on was not increased during medica h bendroflumethiazide in two healthy sub- On the contrary the zinc balances were l in a negative direction in both subjects n th azides The urinary Zn excretion in when thiazides were administered as re efore (7 10) However the increase in uri tput is far too small to completely explain ed balances The percentage of zinc in ch appeared in faeces was increased from ?% in subject A and from 70 to 74% in B

hange in Zn absorption might be due to the on with bendroflumethiazide or to the entat on with potassium chloride The es were strongly positive when Zn tat on was given in periods V and VI In A the percentage of Zn intake appearing in as not higher during period VI when 10 mg flumethiazide was given than during when only 5 mg was administered In B the faeces contained slightly more Zn riod VI than during period V When mag supplementation was given during periods VIII the zinc balances were strongly nega both subjects More Zn than ingested ap in faeces of subject B The explanation may part of the extra Zn load absorbed during V and VII was now excreted to the bowel

clusion The Zn balances in the two healthy changed in a negative direction during nt with bendroflumethiazide combined with m supplementation When both potassium gnesium supplementation was given the balances were strongly negative in both subjects It might be that additional intake of both potassium and magnesium decrease the intestinal absorption of zinc The increased urinary losses of Zn during treatment with diuretics with maintained or in creased serum Zn levels cannot be explained by increased zinc absorption Thus it seems probable that tissues are depleted of zinc during treatment with diuretics

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REFERENCES

1 Naess K Diuretika og ioner Specielt kalsium mag nesium og sink Tidsskr Nor Laegeforen 95 (19-21) 1177 1975
2 Pak C Y C Ruskin B & Diller E Enhancement of renal excretion of zinc by hydrochlorothiazide Clin Chim Acta 39 511 1972
3 Reifenstein Jr E C Albright F & Wells S L The accumulation interpretat on and presentation of data pertaining to metabolic balances notably those of calcium phosphorus and nitrogen J Clin Endocrinol 5 367 1945
4 Schraer K K & Calloway D H Zinc balance in pregnant teenagers Nutr Metab 17 205 1974
5 Steele T H Dissociation of zinc excretion from other cations in man J Lab Clin Med 81 205 1973
6 Wester P O Spårelement vid hypertoni före och under tiazidbehandling (abstract) Paper at the annual meeting of the Swed sh Medical Society Stockholm 1970
7 — Trace elements in serum and urine from hyperten sive patients before and during treatment with chlor thalidone Acta Med Scand 194 505 1973
8 — Trace elements in serum and urine from hyperten sive pat ents treated for six months with chlor thal done Acta Med Scand 196 489 1974
9 — Zinc during diuretic treatment Lancet 1 578 1975
10 — Urinary zinc excretion during treatment with dif ferent diuretics Acta Med Scand 708 709 1980

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Tissue Zinc at Autopsy—Relation to Medication with Diuretics

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ACT Diuretic treatment has been shown to substantial increase in the urinary output of wever, the serum zinc levels remain normal raised In the present study tissue zinc was in liver, kidney and skeletal muscle tissue 17 consecutive autopsies In 90 of the cases uscle and aortic tissue were also studied The lues were correlated to previous treatment retics A lower liver zinc level was observed group of patients who had been on diuretic nt for more than 6 months compared to the without treatment, the difference being highly nt The skeletal muscle zinc was also low in ients who had been on diuretic treatment gard to the metabolic functions of zinc, the lepletion of this element after diuretic treat ay be of clinical importance

ds zinc diuretics liver kidney skeletal muscle uscle aorta

d Scand 208 269 1980

urinary zinc excretion has been found during nt with hydrochlorothiazide (5 14) ben nethiazide (14) chlorthalidone (10 11 14) nide (7 14) bumetanide (14) and triamterene his effect persisted even after long term nt (12) However the serum level of zinc in s treated with diuretics for more than 6 was found to be normal or raised (13) A study of zinc during diuretic therapy de ated that increased zinc absorption was not lequate explanation of maintained or in d serum concentration of zinc despite in d urinary losses A better explanation may be nc is mobilized from tissues causing an intra r zinc deficiency

aim of the present study was to investigate ic content in skeletal muscle heart muscle kidney and aorta at autopsy in patients who en and who had not been on diuretics

MATERIAL AND METHODS

Skeletal muscle liver and kidney tissue were collected from 147 consecutive autopsies From the last 90 of these autopsies a piece of aorta and myocardium were collected as well The skeletal muscle tissue was taken from mus culus psoas major the liver tissue from the superior sur face of the right lobe the kidney tissue from the middle of the lateral part of the right kidney the heart muscle tissue from the anterior wall of the left ventricle and the aortic tissue from the ascending part of arcus aortae The sam ples were kept at −20°C until required for analysis Zinc was determined by atomic absorption (Varian Techtron Model 1100) The tissue samples were dissolved in 2 ml fuming H_2SO_4 and 5 ml H_2O_2

The 147 autopsies were divided into three groups based on causes of death Group A consisted of 49 patients with various causes of death group B of 62 patients whose death was caused by coronary artery disease and group C of 36 patients with various tumors as the cause of death

All records were studied retrospectively with regard to medication with diuretics If information about medication was missing or uncomplete in the records the relatives and/or the house doctor were contacted Based on the diuretics administered (thiazides and/or furosemide) the material was divided into three groups Group I No medication with diuretics could be traced This group consisted of 46 autopsy cases 11 of whom had died from coronary artery disease 16 from various tumors and 18 from other causes Group II Diuretics had been adminis tered for less than 1 month In this group there were 36 cases 30 of whom had died from coronary heart disease 13 from various tumors and 9 from other causes Group III Diuretics had been given for more than 6 months This group consisted of 45 cases 20 of whom had died from coronary artery disease 3 from tumors and 22 from other causes

In patients who had had diseases known to affect the zinc content in various organs the zinc values from this particular organ were excluded from the study Thus 26 liver Zn values 6 in group I 14 in group II 6 in group III were excluded due to liver cirrhoses and/or tumor metas tases of the liver Zinc in kidney was excluded in 35 autopsied patients with regard to kidney diseases most often due to acute cystopyelitis

Student s *t* test was applied in the statistical calcula tions

Table I *Mean values of zinc (µg/g wet weight) in different organs from autopsied patients [illegible] earlier medication with diuretics*

Group A = various causes of death group B = death from coronary heart disease group C = death from [illegible]

Group	Without diuretics	Diuretics <1 month	Diuretics >6 months
Liver tissue			
A	59 9±33 6 (*n*=16)	92 0 63 2 149 8 (*n*=3)	51 3±23 7 (*n*=19)
B	75 3±28 1 (*n*=11)	67 4±24 6 (*n*=26)	49 3±17 5 (*n*=18)
C	108±52 7 (*n*=12)	63 5±27 8 (*n*=13)	41 6 47 8 (*n*=2)
A+B+C	79±45 1	68 7±27 9	49 6±20 1
Kidney tissue			
A	34 3± 6 5 (*n*=12)	39 4±16 9 (*n*=7)	38 2±15 7 (*n*=14)
B	31 6± 9 5 (*n*=7)	35 6±13 3 (*n*=30)	30 4± 7 7 (*n*=14)
C	49 5±24 0 (*n*=12)	37 4± 9 8 (*n*=12)	24 0 27 2 (*n*=[illegible])
A+B+C	39 6±19 0	36 8±12 8	35 0±14 3
Skeletal muscle tissue			
A	49 5±12 3 (*n*=18)	56 5±17 5 (*n*=9)	48 2±11 5 (*n*=22)
B	58 5±14 4 (*n*=11)	52 8±13 8 (*n*=30)	48 7± 9 9 (*n*=20)
C	54 8±16 0 (*n*=16)	55 5±10 4 (*n*=17)	50 0 33 3 47 2 (*n*=3)
A+B+C	53 6±14 4	54 2±13 4	48 0±10 5
Heart muscle tissue			
A	27 2± 4 3 (*n*=12)	30 2± 4 7 (*n*=4)	28 7± 6 3 (*n*=11)
B	29 8± 6 2 (*n*=8)	27 7± 7 1 (*n*=20)	26 7± 7 3 (*n*=1[illegible])
C	34 2±13 3 (*n*=9)	28 7± 5 3 (*n*=8)	17 1 25 7 (*n*=[illegible])
A+B+C	30 1± 8 7	28 1± 6 3	27 2± 6 8
Aortic tissue			
A	25 5± 7 8 (*n*=13)	32 4±13 8 (*n*=4)	28 2±18 8 (*n*=11)
B	28 5±14 5 (*n*=10)	24 5±10 1 (*n*=20)	21 0± 4 5 (*n*=1[illegible])
C	25 6± 4 8 (*n*=9)	29 9±19 1 (*n*=8)	28 3 22 8 (*n*=2)
A+B+C	26 5± 9 6	26 8±13 2	24 5±13 0

RESULTS

The zinc values in the liver kidney skeletal muscle heart muscle and aortic tissues are presented in Table I

The mean zinc value in liver tissue from autopsied patients who had not taken any diuretics was 79 2 µg/g and from those who had been taking diuretics for more than 6 months 49 6 µg/g The difference between these two values is highly significant If only group B (patients who had died from coronary artery disease) is selected among patients who had not taken any diuretics and compared to group B among patients who had taken diuretics for more than 6 months the difference in liver zinc is still significant ($p < 0\ 0025$) There was no significant difference between the group without diuretics and the group who had taken diuretics for less than 1 month Within the group of patients who had not taken any diuretics group C (patients who had died from tumors) had more zinc in the liver than group A (patients who had died from [illegible] causes) Within the groups of patients who had taken diuretics for less than 1 month and [illegible] than 6 months there were no significa[illegible] between groups A B and C

No significant differences in kid[illegible] observed with regard to previous d[illegible] (Table I)

In skeletal muscle the zinc content was [illegible] ($p < 0\ 025$) in patients who had taken d[illegible] more than 6 months than in patients who [illegible] been taking diuretics If group I (without [illegible] plus group II (diuretics for less than 1 m[illegible] compared with group III (diuretics for m[illegible] months) the degree of significance increase[illegible] 0 005)

No significant differences in zinc co[illegible] muscle and aortic tissue were observed w[illegible] to the different diuretic groups There w[illegible] ever a tendency towards lower values [illegible] uretic group

DISCUSSION

...st prominent finding in the present work ... highly significant reduction in liver zinc in ...d patients who had been taking diuretics for ...an six months The mean value and stan...viation for liver zinc in patients who had not ...uretics are in excellent agreement with val... 3 patients who had died from various illnes... whose livers were histologically normal (2) ...r zinc is known to be strongly reduced in ...rhosis and in tumors and tumor metastases ...ver (2 8) This was also true in the present ...ation and 26 liver Zn values were excluded ... study High liver zinc values were noted in ...p C of group I viz patients who had died ...ncer in other parts of the body than the ...his is also in agreement with other studies

...nean liver zinc value in group III (diuretics ...nths) was very low and in agreement with ...d data on liver cirrhosis (8)

...ous studies have revealed that treatment ...azides causes much more extensive losses ...n zinc than treatment with loop-diuretics or ...ene In the present study it was however ...sible to correlate the reduction of tissue zinc ...se of different diuretics because too many ...had used more than one type of diuretics

...recently been pointed out that the serum ...centration is not always a good indicator of ...ficiency (1) There is evidence that the liver ...ncentration may be a more sensitive factor ...receiving zinc-deficient diet the liver zinc ...zinc content in whole blood was reduced ...weeks serum zinc however remained at ...levels (3)

...g total starvation in man the zinc balances ...ongly negative but the serum zinc levels ...al normal (6 9) The liver zinc was how... ...ot studied in these patients Further after ... of the pancreatic duct in rats the liver zinc ...ongly decreased but the serum zinc re... normal (1)

...ms as if the serum zinc does not decrease ...me of the zinc stores primarily in the liver ...en reduced

...e present study the zinc concentration in ... muscle was also significantly reduced ...ndicates that the reduction of tissue zinc in ... on long term diuretics is more extensive ... only restricted to the liver If the zinc reduction in tissues during diuretic treatment causes impairment in the function of various organs or not is unclear Further studies are needed to answer this question However taking into consideration that zinc is an essential element in human metabolism it is probable that the zinc losses are of clinical importance

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REFERENCES

1 Abdullah M & Ihse I Utesluter normalt zinc i serum zinkbrist? Lakartidningen 73 2104 1976
2 Kew M C & Mallet R C Hepatic zinc concentrations in primary cancer of the liver Br J Cancer 29 80 1974
3 Mathur A Wallenius K & Abdullah M Zinc concentrations in fluid and tissues after prolonged feeding of zinc deficient diets in rats Lakartidningen 73 2104 1976
4 Olson K B Heggen G E & Edwards C F Analysis of 5 trace elements in the liver of patients dying of cancer and non-cancerous diseases Cancer N Y 11 555 1958
5 Pak C Y C Ruskin B & Diller E Enhancement of renal excretion of zinc by hydrochlorothiazide Clin Chim Acta 39 511 1972
6 Spencer H & Samachson J Studies of zinc metabolism in man In Trace element metabolism in animals (ed C F Mills) p 312 Livingstone Edinburgh 1970
7 Steele T H Dissociation of zinc excretion from other cations in man J Lab Clin Med 81 205 1973
8 Vallee B L Wacker W F C Bartholomay A F & Hach F L Zinc metabolism in hepatic dysfunction II Correlation of metabolic pattern with biochemical findings N Engl J Med 257 1055 1957
9 Wester P O Spårelement före under och efter totalsvalt (abstract) Paper at the annual meeting of the Swedish Medical Society Stockholm 1969
10 — Spårelement vid hypertoni före och under tiazid behandling (abstract) Paper at the annual meeting of the Swedish Medical Society Stockholm 1970
11 — Trace elements in serum and urine from hypertensive patients before and during treatment with chlorthalidone Acta Med Scand 194 505 1973
12 — Trace elements in serum and urine from hypertensive patients treated for six months with chlorthalidone Acta Med Scand 196 489 1974
13 — Zinc during diuretic treatment Lancet 1 578 1975
14 — Urinary zinc excretion during treatment with different diuretics Acta Med Scand 208 209 1980
15 Wright E B & Dormandy T L Liver zinc in carcinoma Nature 237 166 1973

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Effects of Mefruside Treatment in Hypertension

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ACT Fifty two middle aged patients with es- hypertension were treated for five months 5 mg mefruside as the only antihypertensive Blood pressure, heart rate fasting blood glu holesterol triglycerides uric acid, electrolytes ght were controlled regularly before and dur atment Blood pressure normalized in 43 cases) The decrease was more marked in the s and their maximal response appeared later ificant changes were seen in cholesterol and rides Serum uric acid levels increased sig tly in both sexes ($p<0.001$) but no patient ed gout A significant decrease ($p<0.001$) in potassium was seen only one male, with y for diabetes mellitus showed a decreased tolerance

rds essential hypertension non alcoholics mef metabolic effects sex differences

ed Scand 208 273 1980

ent of hypertension has attracted great in especially since the demonstration that com normotension might be achieved in a large of patients with severe hypertension (22) al primary screening trials are in progress in n and the results indicate decreases in mor as well as mortality (5)

ng the 50s and 60s diuretics of the thiazide were used as the drug of choice Treatment β-blockers was introduced during the 70s and re now the drugs of choice in the Scandina countries together with diuretics The early 0 saw the introduction of low-dosage thiazide ent (3) but its long term evaluation is not yet ete

effects from saluretics with glucose intoler and possible development of diabetes gout hypopotassemia are well known and lead to rawal of the drug in 5–15% of patients (8 10 14 17 19 21 26) New data may indicate other long term side effects can appear on treatment with thiazide diuretics In two controlled studies (1 2) cholesterol and triglycerides were significantly elevated during treatment with chlor thalidone and hydrochlorothiazide but these results are contradicted by others (16) Spironolactone is a valuable alternative to thiazide treatment especial ly when hypopotassemia glucose intolerance or gout have developed

Mefruside (Baycaron®) has been available on the Swedish pharmaceutical market since 1971 (7 8 9 19) Mefruside is chemically closely related to thiazides but it has been claimed that intracellular potassium and magnesium depletion is less pro- nounced (8) It remains to be confirmed whether these intracellular findings prevail during long term treatment Several authors claim that treatment with mefruside gives rise to less side effects as re gards glucose intolerance hypopotassemia and hypomagnesemia (6 9 19 26) The antihyperten sive effect of mefruside in a single dosage of 25 mg daily has been well documented (7 8 21)

In view of the reported significant increases in cholesterol and triglycerides during therapy with thiazides and thiazide like diuretics this investiga tion was undertaken to study partly the metabolic effects of mefruside and partly the sex related an tihypertensive effect

PATIENTS

Only 40–65 year-old patients with a diastolic blood pres- sure (BP) on three visits of ≥100 mmHg after 10 min in the supine position and a mean heart rate of <90 beats/min were included in the study The 52 patients (26 males 26 females) were selected from five out patient clinics in the city of Malmo (240 000 inhabitants) All had denied a his tory of alcohol overconsumption

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Table I *Blood pressures (mmHg) and heart rates (HR) (beats/min) before and during therapy with mefruside 25 mg once daily (mean ± 1 S D)*

	Males (n=26)						Females (n=26)	
	Supine			Erect			Supine	
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP
Before therapy*	160 4±15 0	103 5±5 6	72±9	156 0±19 1	106 3±8 0	79±9	176 5±18 6	[illegible]
During therapy								
1 month	144 6±16 1	94 2±6 7	76±9	140 4±18 7	98 5±8 8	82±9	155 1±15 9	[illegible]
3 months	143 8±16 8	93 5±7 2	72±9	140 0±18 5	98 8±7 8	81±9	147 2±13 5	[illegible]
5 months	141 3±16 7	91 0±7 1	71±9	139 0±20 1	97 0±9 0	77±9	145.5±15 3	[illegible]
p (*t* test)	***	***	N S	***	**	N S	***	*

* BP before treatment is calculated as the mean of three visits
N S = not significant ** $p<0.01$ *** $p<0.001$

METHODS

The BP was measured with a calibrated mercury manometer by nurses Diastolic BP defined as phase V according to Korotkoff was measured initially in both arms and at later controls in the arm with the highest diastolic pressure The measurement was done after 10 min in the supine and after 1–2 min in the standing position together with heart rate The treatment consisted of 25 mg mefruside (Baycaron®) daily during the breakfast Controls after 1 3 and 5 months of therapy were done during fasting conditions in the morning together with the following parameters BP plasma concentrations of sodium potassium creatinine calcium albumin magnesium blood glucose cholesterol triglycerides and uric acid The [illegible] controlled for glucose protein and blood

If fasting blood glucose rose during treatment [illegible] above the upper normal limit (5 6 mmol/l) serum [illegible]sium decreased to values below 3.5 mmol/l or magnesium to values below 0 70 mmol/l the [illegible] were repeated together with an oral glucose [illegible] test (1 g glucose/kg b wt) If this showed a [illegible] result mefruside administration was discontinued [illegible] new tolerance test was carried out after two [illegible] potassium was given orally only if an [illegible] hypopotassemia was present

The metabolic parameters were measured [illegible] methods of the Central Laboratory at [illegible] Hospital The following normal ranges have been [illegible] S-Na 131–151 mmol/l S-K 3 5 5 0 mmol/l [illegible] 2 20–2 60 mmol/l S Mg 0 70–1 10 mmol/l S-[illegible] 60–115 μmol/l S-triglycerides 40–60 years 0 [illegible] S-cholesterol ≤7 70 mmol/l fasting blood glucose [illegible] mmol/l S-albumin 40–52 g/l

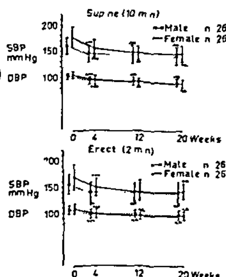


Fig 1 Systolic (*SBP*) and diastolic (*DBP*) BP before and during therapy with mefruside 25 mg once daily Note that each mean BP is compared with the previous control during therapy *** $p<0.001$ ** $p<0.01$ * $p<0.05$ n s = not significant

RESULTS

Effects on blood pressure

Results for BP and heart rate are shown [illegible] and Table I Systolic BP supine and [illegible] females before treatment was significantly [illegible] than in males ($p<0.01$) but there was no [illegible] difference in either the systolic or the diastolic [illegible] both supine and erect after 5 months of treatment [illegible] The decreases in both systolic and diastolic [illegible] supine and erect during the first month and [illegible] the two following months were significantly [illegible] pronounced in females than in males (after 1 [illegible] $p<0.05$ after 3 months $p<0.01$) Heart rate [illegible] supine position was similar in both sexes [illegible] control it was 6–9 beats higher in the [illegible] position ($p<0.05$)

DBP	HR
109 8+9 8	8?+10
99 1±8 5	83+11
94 6+6 1	80+10
95 5+7 7	8?+10
	N S

tand ng systolic BP was lower on average sup ne in both sexes both before and during but the opposite applied for the diastolic I)

fi e months of treatment BP in both supine ing pos t on had decreased in all but two (3 5%) Seven patients (13%) still had a liastol c BP of >100 mmHg they received d therapy with β blockers after the study in completed Two other patients had a d astol c BP of >100 mmHg but both had a sup ne diastol c BP and they continued with le after the study Both supine and standing nal zed in 43 pat ents (82 7%) during mef reatment in a dose of 25 mg daily

Ic effects

ults for the metabolic parameters are shown : II

blood glucose

ent had an overt diabetes mellitus As n Table II no signif cant increase in fasting lucose occurred in males or females In six s (♂ 4 ♀ 2) the fasting blood glucose rose 5 6 mmol/l and they were examined with an cose tolerance test (1 g glucose/kg) This s normal in all but one patient a 50-year old th a hered tary background for diabetes His nt w th mefruside was withdrawn after five three weeks later a new glucose tolerance s normal The fasting blood glucose values in ter f ve pat ents after 5 months of therapy were normal During the study the weight of the individual patient changed considerably and no significant correlation was found between weight and fasting blood glucose at any control Neither was there any signif cant correlation between changes in serum potass um and blood glucose (12)

Serum potassium

Serum potassium decreased significantly in both sexes ($p<0\ 001$) Two patients showed hypopotassemia one of them with concurrent hyperglycemia One male had hypopotassemia (3 4 mmol/l) at the start of the study and S K^+ decreased to 2 9 mmol/l but he had a normal oral glucose tolerance test After the study he continued with mefruside together with potassium tablets He may have an endocrine type of hypertension but further investigation is not complete

Serum uric acid

Serum uric acid increased in both sexes ($p<0\ 001$) No patient developed clinical signs of gout during therapy One patient had an increased value initially (530 μmol/l) with a further increase during therapy to 601 μmol/l and he was subsequently treated with allopurinol (Zyloric®)

Serum cholesterol

Serum cholesterol was measured before and after 5 months of therapy No patient developed hypercholesterolemia and the blood levels were unchanged in both sexes Ultracentrifugation stud es were not carried out

Serum triglycerides

The serum triglycerides did not show any significant change Five patients had an initial hypertriglyceridemia two returned to normal values and three were unchanged (25) There was a positive but non significant correlation ($r-0\ 23$) between changes in weight and serum triglycerides

Serum calcium

Serum calcium did not change s gn f cantly and no patient developed hypercalcemia which is known to occur during therapy with thiazides (11 23 24)

Plasma albumin

In males there was a significant drop in plasma albumin ($p<0\ 05$) but not in females

Table II *Results from metabolic investigations of blood and changes in body weight durin[g] treatment with 25 mg mefruside daily (mean ± 1 S D)*

	Fasting blood sugar (mmol/l)	Potassium⁺ (mmol/l)	Uric acid (μmol/l)	Cholesterol (mmol/l)	Triglycerides (mmol/l)	Calcium (mmol/l)	[illegible]
Females							
Before therapy	4 8±0 7	4 2±0 4	250±58	6 1±1 1	1 29±0 53	2 36±0 17	[illegible]
During therapy							
1 month	5 1±0 9	3 8±0 4	308±86	–	–	2 39±0 13	[illegible]
3 months	4 8±0 8	3 8±0 4	312±75	–	–	2.40±0 13	[illegible]
5 months	4 8±0 7	3 9±0 4	309±64	6 3±0 8	1 46±0 61	2 40±0 11	[illegible]
p (*t* test)	N S	***	***	N S	N S	N S	[illegible]
Males							
Before therapy	4 5±1 1	4 3±0 4	325±75	5 7±1 3	1 35±0 58	2 45±0 11	[illegible]
During therapy							
1 month	4 9±1 2	3 9±0 3	383±68	–	–	2 41±0 17	[illegible]
3 months	4 9±1 0	3 9±0 4	399±102	–	–	2 45±0 17	[illegible]
5 months	4 9±1 0	3 9±0 4	377±86	5 7±1 1	1 47±0 69	2 45±0 17	[illegible]
p (*t* test)	N S	***	***	N S	N S	N S	[illegible]

N S = not significant * $p<0\ 05$ *** $p<0\ 001$

Serum magnesium

No significant changes were seen in either sex None of the patients developed hypomagnesemia (6 18)

Serum creatinine

Serum creatinine decreased but not significantly Four patients developed an increase over the upper normal limit with a subsequent decrease into the normal range

Urine investigations

None of the patients developed glucosuria, proteinuria or hematuria during the treatment One patient had slight proteinuria before the therapy this disappeared later and an i v urography was normal

Weight

No significant change in weight was found in either sex during 5 months of mefruside therapy though there were considerable intraindividual variations

Other metabolic parameters

Controls of hemoglobin ESR and serum sodium showed no significant changes

DISCUSSION

The value of mefruside as an antihypertens[ive] has been demonstrated in several studies [but] metabolic effects especially on plasma lipid[s have] not been studied earlier in a comparativ[ely] population of both sexes

Mefruside induces a significant decre[ase in] serum potassium but the frequency of [hypo]potassemia after 5 months of therapy se[ems to] be low (2–4%) as no general substitution [was] given A surprising finding was that fasting [blood] glucose did not increase significantly and o[ne] of six glucose tolerance tests in hypergly[cemic pa]tients was pathological Conn (12) and Mor[…] (20) have suggested that a pathological gluc[ose tol]erance test during therapy with diuretics [can be] normalized by means of substitution with [potas]sium but other authors could not verify the[se find]ings (27) This study supports the possibility [that in] addition to exposure to diuretics develop[ment of] mature onset diabetes may require a gen[etic pre]position for diabetes

In this investigation neither cholesterol [nor tri]glycerides increased significantly in contr[ast to] therapy with chlorthalidone and hydro[chloro]thiazide (1 2) Seasonal variations in fasting [blood] glucose, blood lipids and serum uric acid are known and can interfere with a compar[…]

Crea nine (µmol/l)	We ght (kg)
84+13	71 3+13 ?
79+1?	70 7+14 6
N S	N S
101+13	8? 0+9 5
96 17	8? 0+8 3
N S	N S

erm study such as this (15) All the present started the treatment during the autumn and completed t during the spring
m magnes um d d not change significantly th rapy wh ch conf rms some results of ear s on mefrus de (6) Intracellular depos ts ssium were not stud ed Some authors have ted that many patients who developed d a on d u et cs had low magnesium values in but th s could be an effect of the develop- f diabetes (10) The changes in serum mag n the present patients were very small and t correla e with the changes in fasting blood e
m ca c um d d not change beyond the normal in any of the pat ents Several studies have that serum calc um may increase during c therapy and n some pat ents even lead to alcem a (23 24) It is suggested in a recent (11) that the pat ents who develop hypercal of en have a latent hyperparathyro dism decrea e in plasma albumin during therapy e a result of a s gn ficantly lower BP because ifican ly elevated plasma prote n level has demonstrated n middle aged males with an ished hypertens on and is considered partly to esu t of hemoconcentration (25)
onclus on 25 mg mefruside given daily during five months to a m ddle aged population of non al coholic hypertensive pat ents results in both supine and standing normotens on in the overwhelming majority with few of the metabol c alterat ons that are normally seen especially in non treated and unselected hypertensive males (4)

REFERENCES

1 Ames R P & H ll P Elevat on of serum l p d levels during d uret c therapy of hypertens on Am J Med 61 748 1976
2 — Increase in serum l p ds during the treatment of hypertens on with chlorthal done Lancet I 721 1976
3 Berglund G & Andersson O Low doses of hydrochlorothiazide in hypertens on Ant hypertens ve and metabol c effects Eur J Cl n Pharmacol 10 177 1976
4 Berglund G Larsson B Andersson O Larsson O Svardsudd K Bjorntorp P & Wilhelmsen L Body compos t on and glucose metabol sm in hypertensive m ddle aged males Acta Med Scand 200 1963 1976
5 Berglund G W lhelmsen L Sannerstedt R Hansson L Andersson O S vertsson R Wedel H & Wikstrand J Coronary heart-d sease after treatment of hypertens on Lancet I 1 1978
6 Bergstrom J Hultman E & Solheim S B The effect of mefrus de on plasma and muscle electrolytes and blood pressure in normal subjects and n pat ents w th essent al hypertension Acta Med Scand 194 427 1973
7 Bevegård S Castenfors J & Dan elsson M Haemodynam c effects of four months mefrus de therapy in hypertensive pat ents Acta Med Scand 201 93 1977
8 Broman J Coll ng J Dafgård T Elander J Helander S Helldorff I Jaderberg E L dstrom P Lindahl T Luhr R Modee J Nandorf R Nerell G Sandefeldt Å Sjogren S Than ng T & Tre s F Effekt av mefrus d på blodtryck och på kal um magnes um och urinsyra i serum Lakart d n ngen 72 1714 1975
9 Cantor R A double bl nd cross-over double dummy trial to compare the eff cacy of mefrus de (Baycaron) and chlorthal done (Hygroton) n the treatment of geriatric pat ents w th pers stent hyper tens on In Sympos um on Hypertens on pp 119–125 Saltsjobaden Uppsala 1975
10 Chazan J A & Boshell B R Et olog cal factors in th az de induced or aggravated d abetes mell tus D abetes 14 132 1965
11 Christensson T Hypercalcem a in a health screen ng Stud es of prevalence relat on to sex and age causes and man festat ons w th special reference to blood pressure Thesis Stockholm 1976
12 Conn J W Hypertens on the potass um ion and impa red carbohydrate tolerance N Engl J Med 273 1135 1965

13 Greybiel A L & Sode J Diuretics potassium depletion and carbohydrate intolerance Lancet 2 1265 1971
14 Hicks B H Ward J D Jarret R J Keen H & Wise P A controlled study of clopamide clorexolone and hydrochlorothiazide in diabetics Metabolism 22 101 1973
15 Johansson B W & Senturia J B Seasonal variations in the physiology and biochemistry of the European hedgehog (Erinaceus europeans) including comparisons with non hibernators guinea pig and man Acta Physiol Scand (Suppl) 380 1974
16 Kannel W B Gordon T & McGee D Diuretics and serum cholesterol Lancet 2 1362 1977
17 Lewis P J Petrie A Kohner E M & Dollery C T Deterioration of glucose tolerance in hypertensive patients on prolonged diuretic treatment Lancet 1 564 1976
18 Lim P & Jacob E Magnesium deficiency in patients on long term diuretic therapy for heart failure Br Med J 3 620 1972
19 Lund Johansen P Effekten av mefrusid (Baycaron) och polythiazid (Renese) på serumelektrolytter og dagligivets blodtrykk hos menn med essensiell hypertensjon In Diuretica og hypertensjons symposium (ed Bayer Kjemi A S) pp 113–121 Adolf L Nielsen Oslo 1971
20 Mortan C Rapaport J & Hurd H F Thiazide induced glucose intolerance treated with po[illegible] Arch Intern Med 113 405 1964
21 Murdoch W R & Auld W H R Mefru[illegible] clinical practice A study of electrolyte a[illegible] d h[illegible] sive effect Br Med J 4 786 1971
22 Schroeder H A Control of hyperten[illegible] hexamethonium and 1 hydrazinophathalazine [illegible] Intern Med 89 523 1952
23 Seitz H & Jaworski Z Effect of [illegible] chlorothiazide on serum and urinary cal[illegible] urinary citrate Can Med Assoc J 90 414 196[illegible]
24 Van der Slugs Veer J Birkenhager J C & S[illegible] D Effect of orally administered diuretics on [illegible] metabolism Proceedings of the Fourth Eu[illegible] Symposium on Calcified Tissues March 28th [illegible] 1st 1966 Leiden the Netherlands Found[illegible] Congress series Excerpta Medica 170 96 19[illegible]
25 Tibblin G Bergentz S E Bjure J & Wilhe[illegible] L Hematocrit plasma protein plasma vol[illegible] viscosity in early hypertensive disease Am [illegible] 72 165 1966
26 Waal Manning H J Effect of equivalent an[illegible] tensive doses of mefruside and cyclopenthia[illegible] serum electrolytes uric acid and glucose toler[illegible] hypertensive patients Clin Exp Pharmacol [illegible] 2 141 1975
27 Wacker W E C & Parisi A F Mag[illegible] metabolism N Engl J Med 278 712 and 77[illegible]

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Increased Urinary Protein Excretion after Intravenous Injection of Furosemide in Man

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ACT The furosemide induced increase in excretion, and its relations to 1) the size of molecules as reflected by three enzymes and erular filtration rate (GFR), plasma renin (PRA) and prostaglandin (PG) E_2 and $F_{2\alpha}$ ns were studied in 14 outpatients with normal nction and 13 healthy males Furosemide (120 given intravenously, and thereafter the pro-retion and the above parameters were moni r 1-2 hours In both groups, furosemide transient increase in protein excretion The n of the largest molecule, β glucuronidase, 6.3-fold while those of N acetyl β D gluco-ase and of the smallest molecule, α amylase, d by 91 and 37% respectively GFR in , too, but markedly less than the protein n PGE and $PGF_{2\alpha}$ excretions increased an GFR and changed simultaneously with the n of proteins Furosemide also caused a increase in PRA This lasted however, much han the rise in PG and protein excretion or The results suggest that the furosemide in crease in protein excretion is 1) related to the ar size of proteins 2) partly due to the rise in) simultaneous with the change in PG ex Our findings also agree with the view osemide causes changes in glomerular perme

ds furosemide protein excretion glomerular fil ate plasma renin activity prostaglandin excre

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nide has been found to raise the excretion of rotein molecules in urine (6 7 13) Among ther determinants transglomerular passage omolecules in general is related molecular In addition to water and electrolyte excre rosemide increases renal blood flow (8 24 possible cause of the augmented protein n The increase in renal blood flow has been attributed at least partly to augmented renal production (25) and urinary excretion of vasodila tory prostaglandins (PG) (12 18 19 23) Moreover furosemide raises plasma renin activity (PRA) (8 14 23) which results in elevated angiotensin II concentration in plasma This increases the excre tion of macromolecules (2) Therefore we decided to study in man 1) the effect of furosemide on the urinary excretion of proteins of various sizes as reflected by three different enzymes and 2) the relations of furosemide induced proteinuria to glomerular filtration rate (GFR) PRA and urinary PG excretion

METHODS

After an overnight fast and a recumbency of two hours 120 mg of furosemide (Furesis® Laake Turku Finland) was administered intravenously in five minutes to two different groups of subjects Just before the furosemide injection and during the course of the experiment the subjects drunk hourly 200 ml of water All subjects were voluntary and gave their consent to the study

Group I consisted of 14 outpatients (9 males and 5 fe males aged 22–50 years) who were examined for var ious dyspeptic complaints They had normal renal func tion and no obvious proteinuria After the furosemide injection blood samples were taken at 0 15 30 45 and 60 min via an injection needle which was introduced into a cubital vein for the period of the experiment For the time between samplings the needle was filled with saline Urine was collected for one hour just before the drug administra tion and thereafter every 15 min during one hour The parameters measured were as follows urine excretion rate creatinine clearance unreabsorbed fraction of filtered Na^+ total excretion of proteins and the excretion of three enzymes (β glucuronidase N acetyl β D glucosamini dase (NAG) and α amylase the molecular weights of

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Abbreviations GFR=glomerular filtration rate PG=pros taglandin PRA=plasma renin activity NAG=N acetyl β D-glucosaminidase Na^+=sodium

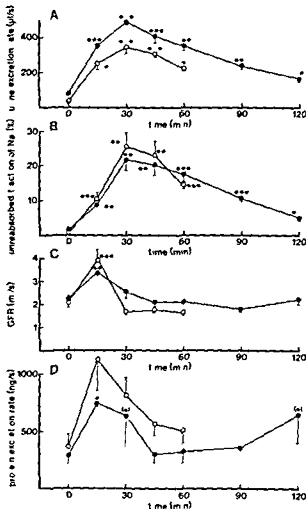


Fig 1 Effect of furosemide (1?0 mg i v) on the mean (+S E) urinary excretion rate (A) unreabsorbed fraction of filtered Na (B) GFR (C) and protein excretion rate (D) in 14 patients with normal renal function (●—● group 1) and 13 healthy males (○—○ group 2) * $p<0.1$ * $p<0.05$ ** $p<0.01$ *** $p<0.001$ compared to the values just before furosemide injection (0-values)

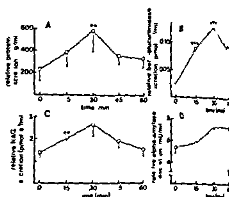


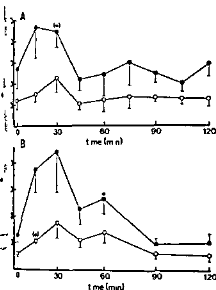
Fig 2 Effect of furosemide (1?0 mg i v) on the (±S E) relative protein (A) β glucuronidase (B) (C) and α amylase (D) excretion (relative excretion rate/GFR) in 14 patients with normal renal function (group 1) * $p<0.05$ ** $p<0.01$ * $p<0.0$ compared to the values just before furosemide inj. values)

which are 218000 160000 and 55000 respectively) GFR was estimated as endogenous creatinine clearance

Group 2 consisted of 13 healthy males (aged 20–27 years) After the furosemide injection blood samples and urine were collected every 15 or 30 min for two hours as in group 1 PRA and the above parameters except for the three enzymes were measured in all subjects In five of them (*subgroup 2 A*) $PGF_{2\alpha}$ excretion in urine was also measured In the seven other subjects (*subgroup 2B*) the effects of a PG synthetase inhibitor on the furosemide induced proteinuria and the alterations in PRA and PGE excretion were studied That is why the seven subjects in subgroup 2B underwent twice the furosemide treatment in a cross-over manner with and without indomethacin premedication (50 mg orally two hours before the furosemide

injection Indetnt[3] Medica Helsinki Finland interval between the trials was at least seven days

For estimation of PRA blood samples were into cooled test tubes containing 0 1 N Na EDTA wise the samples were taken into dried test tubes (for determination of $PGF_{2\alpha}$ as 33% alcohol solu plasma or serum samples were stored a below until analyzed The activities of β glucuronidase and α amylase were measured from urine samples at 4 C Total protein was determined from TCA tate using Folin Ciocalteau reagent (modified Lowry et al (10)) Creatinine in serum and urine measured by the method based on the Jaff reaction The activity of β glucuronidase was estimated by a modified method of Talalay et al (?0) It is based colorimetric determination of phenolphthalein from the substrate phenolphthalein β-D-glucuronide by the action of β glucuronidase The activity was determined using p-nitrophenyl-N acetyl-glucosamine as substrate the released p-nitrophenol yellow and its absorbance was read at 420 nm method of Banerjee & Basu (1)) Alpha amylase was tested with Phadebas amylase kit where the of the measuring enzyme is a starch polymer pressed form (Pharmacia Diagnostics Uppsala PRA was determined by radioimmunoassay of angiotensin I released in incubation according to the method by Fyhrquist et al (4) PGs were extracted by of Unger et al (??) and measured radioimmunologically (9) To separate the free and bound hapten antigen–antibody complex was incubated with a body to rabbit gammaglobulin and polyethylene was added Recoveries were monitored using PGE_1 The cross reactivity of the $PGF_{2\alpha}$ antiserum cal Assays Cambridge Mass) was less than 0.C PGE PGA and PGB at the 50% binding level The reactivity of PGE antiserum (Steranti Research bans England) was as follows PGE 100% PGE



...ffect of furosemide (120 mg i v) (*A*) on the mean $PGF_{2\alpha}$ excretion rate (●—●) and relative $PGF_{2\alpha}$ ... (○—○) (relative excretion excretion rate/ ... healthy males (subgroup 2 A) and (*B*) on the ...cretion rate (●—●) and relative PGE_2 excretion ... in seven healthy males (subgroup 2B) $p<0.1$ compared to the values just before furosemide (0-values)

... PGA 21% $PGF_{2\alpha}$ 6 1% PGB_2 5 5% 6-oxo ...was not measured

...s and standard errors (S E) were calculated and ...ist al significance between the means was ...d by paired *t* test Regression equations were cal... by the method of least squares

RESULTS

...groups furosemide increased the mean uri...cretion rate by 6–10-fold and the unreab... fraction of Na from 0 6–1 7 to 21 7–25 5% ... creatinine clearance) rose by 51–89% and ...tein excretion rate by 155–205% The rise in ...tein excretion rate occurred simultaneously ...increase in GFR but it lasted somewhat than that of GFR The effects of furosemide above parameters are seen in Fig 1

...oup 1 the mean protein excretion rate/GFR ...e excretion) increased by 152% after the ...mide injection (Fig 2) Beta glucuronidase ...as the highest molecular weight among the ...s studied had a 6 3 fold increase in its rela... excretion The relative excretion of NAG rose ...% and that of the smallest enzyme α ... by 37%

In group 2 the mean relative protein excretion increased by 112 and 124% ($p<0.1$) respectively in urine fractions collected 0–15 and 15–30 min after the furosemide injection $PGF_{2\alpha}$ (subgroup 2 A) and PGE_2 (subgroup 2B) excretion rates increased simultaneously with GFR and the protein excretion rates (Fig 3 Fig 1*C* and *D*) The excretion of PGE_2 increased more markedly than that of $PGF_{2\alpha}$ PG and protein excretions remained at the increased level for a longer time than GFR The relative excretion of PGs (excretion rate/GFR) had also increased significantly and was maximal in the same urine fractions as those of proteins and enzymes (Fig 2) Within neither subgroup did the protein excretion rates however correlate significantly with the $PGF_{2\alpha}$ and PGE_2 excretion rates After the furosemide injection PRA showed a pronounced and persistent rise (Fig 4) Within group 2 the changes in PRA did not correlate at all with the alterations in GFR and absolute or relative protein excretions

In subgroup 2 B a single oral pretreatment dose of indomethacin (50 mg) did not inhibit markedly the furosemide induced increase in PGE. Neither did it modify protein excretion in urine fractions collected before or after the furosemide injection Indomethacin did not suppress significantly the increase in GFR and urine excretion rate either It antagonized however effectively the furosemide induced increase in PRA (Fig 4)

DISCUSSION

Furosemide in a dose of 120 mg i v increased markedly the total excretion of proteins and the ex

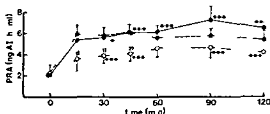


Fig 4 Effect of furosemide (120 mg i v) on the mean (±S E) PRA in 13 healthy males (●—● group 2) = PRA in seven subjects (subgroup 2B) who underwent furosemide treatment with (O) and without (●) indomethacin premedication (50 mg orally two hours before furosemide inject on) in a cross-over manner $^*p<0.05$ $^{**}p<0.001$ compared to the values just before furosemide injection (0-values) $p<0.05$ ‡ $p<0.01$ compared to the means without indomethacin premedication

cretion of three enzymes with different molecular weights in urine The excretion of β glucuronidase with the largest molecular size increased most and that of the smallest molecule α amylase rose least This agrees with our previous findings that the furosemide induced increase in macromolecule excretion is related to molecular size (13)

The increase in protein excretion caused by furosemide has been found to correlate with the rise in GFR (15) In our study the protein excretion rate also increased simultaneously with GFR The rise in GFR can however only partly explain the increased protein excretion rate since the relative protein excretion (excretion rate/GFR) was also elevated and maximal in the 15 30-minute urine fraction when GFR had already returned to the initial level As discussed elsewhere (13) the possible inhibition by furosemide in tubular protein reabsorption seems neither to explain the furosemide induced proteinuria In that study the excretion of high molecular weight proteins was shown to have increased significantly compared with that of low molecular weight proteins which are the ones that should be easily influenced by changes in tubular handling In addition in the present study the rise in protein excretion was of a shorter duration than the inhibition of Na reabsorption or the enhancement of the urinary excretion rate NAG and β glucuronidase have been shown to originate also from the renal tissue itself especially in connection with renal injuries (5 11 16) In this study the tubular origin of the increased enzyme excretion after furosemide cannot be excluded but a much more marked rise in the excretion of large molecules than in that of small ones counteracts the idea that the increase in enzymuria results exclusively from tubular cells Thus the current findings agree with the view that furosemide increases the glomerular permeability for serum proteins

Furosemide increases renal blood flow (8 24 25) a possible cause of the rise in GFR This increase in blood flow has been found to be associated with the augmented excretion of vasodilatory PGs (12 18 19 23) In this study furosemide raised the excretion of both the vasodilatory PGE_2 and the vasoconstrictive $PGF_{2\alpha}$ but the excretion of PGE_2 increased more markedly than that of $PGF_{2\alpha}$ PG excretions remained however elevated for a longer time than GFR The increase in GFR if mediated by vasodilatory PGs could thus be antagonized by some unknown factor(s) activated e g by the intrarenal production of the PGs [illegible]selves The renin-angiotensin system is [illegible] possible candidates It is known to a[illegible] influence of PGs and to be activated by the[illegible] 17) In our study PRA actually increased [illegible]taneously with the excretion of PGs and GF[illegible] showed a persistent rise until the end of the [illegible] period while PGs had returned to the in[illegible]

Indomethacin in a dose of 50 mg thr[illegible] daily has recently been reported to decl[illegible] excretion in patients with proteinuria Th[illegible] been suggested to be associated with ch[illegible] renal haemodynamics by indomethacin as a [illegible] of the decrease in PRA and PG synthesis [illegible] our subjects PG excretion but not PRA ex[illegible] an alteration pattern similar to the prot[illegible] enzyme excretion after the furosemide in[illegible] Thus we may propose that furosemide [illegible] protein excretion is closely associated with PG production but not with PRA. The pro[illegible] further supported by our finding that the [illegible] methacin dose which was incapable of su[illegible] PG excretion essentially inhibited the ris[illegible] but did not modify the protein excretion [illegible] phase of the study The lack of correlation be[illegible] the changes in PG and protein excretions of [illegible] dividual subjects within the experimental [illegible] does not however fit well with this assu[illegible]

In conclusion intravenously administered [illegible] semide increases transiently the urinary [illegible] excretion which is related to the molecular [illegible] proteins The changes in protein excretio[illegible] simultaneously with the change in PG excre[illegible] are partly due to the changes in GFR The [illegible] also agree with the view that furosemide [illegible] the permeability of glomerular capillaries [illegible] macromolecules

ACKNOWLEDGEMENT

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REFERENCES

1 Banerjee D K & Basu D Purification of [illegible] human urine N acetyl-β hexosaminidase A [illegible] chromatography Biochem J 145 113 197[illegible]
2 Brenner B M Bohrer M P Baylis C & De[illegible] M Determinants of glomerular permselectiv[illegible] sights derived from observations in vivo Kid[illegible] 12 229 1977

L C, Jr & Thompson H L Determ nation reatine and creatin ne in urine Anal Chem 8 1949

F Soveri P Puutula L & Stenman L Radioimmunoassay of plasma ren n act vity Chem 22 50 1976

H C Kramer H J & Schap ro A E β-glucoronidase act vity in renal d sease In ern Med 13 6 1973

S & Munro A J Furosem de and renal excre on Br Med J 18 143 1978

M & Raab W Das Verhalten der mak nita en im Harn bei Veränderung der Was Ionenansche dung Cl n Ch m Acta 78 61

J B & Bail e M D Release of vasoact ve from the k dney by d uret cs J Cl n Phar 11 673 1977

B M Sm th J W Newton W T & Parker Rad ommunoassay for prostagland ns Sci 1 494 1971

O H Rosebrough N J Farr A L & R J Prote n measurement w th the Fol n ol reagent J B ol Chem 193 265 1951

M A Jones N F Ziroyannis P N & S M Detect on of renal artery stenos s by ning urinary N acetyl beta D glucosam n dase J 18 414 19 8

E & Anggård E D fferent effects of furo- on urinary excret on of prostagland n E_2 in rabb ts Acta Phys ol Scand 105 367 1979

A Petterson E & Klockars M Effect of furosem de on the urinary excret on of some plas proteins Nephron 22 551 1978

R V Mookerjee B K Bentzel C J P E Babej M & Lee J B Antagon sm of effects of furosemide by indomethacin in normal hypertens ve man Prostaglandins 10 649 1975

V K G Gandhi V C Sharma B K Smith E C & Dunea G Effects of hydration and furosemide given intravenously on proteinuria Arch Intern Med 130 90 1972

16 Proctor R A & Kunin C M Sal cylate induced enzymuria Comparison with other ant inflammatory agents Am J Med 65 987 1978

17 Saynävalammi P Pyykonen M L Yl talo P & Vapaatalo H Prostagland ns in the regulation of cir culation and blood pressure Med B ol 57 157 1979

18 Scherer B Schnermann J Sofroniev M & Weber P C Prostagland n (PG) analys s in urine of humans and rats by d fferent rad oimmunoassays effect on PG-excret on by PG synthetase inh b tors lapa rotomy and furosemide Prostagland ns 15 255 1978

19 Scherer B & Weber P C T me dependent changes in prostagland n excret on in response to furosem de in man Cl n Sci 56 77 1979

20 Talalay P Fishman W H & Huggins C Chromogen c substrates II Phenolphthalein gluc uronic ac d as substrate for assay of glucuroni dase activity J B ol Chem 16 757 1946

21 T ggeler G W L Hulme B & Wydeveld G A B Effect of indomethacin on glomerular permeab l ty in the nephrotic syndrome K dney Int 16 317 1979

22 Unger G W Stamfold I F & Bennett A Extrac tion of prostagland ns from human blood Nature (Lond) 233 336 1971

23 Weber P C S herer B & Larsson C Increase of free arachidonic ac d by furosem de in man as the cause of prostagland n and ren n release Eur J Phar macol 41 329 1977

24 Williamson H E Bourland W A & Marchand G R Inh b t on of furosem de induced increase in renal blood flow by indomethacin Proc Soc Exp B ol Med 148 164 1975

25 W ll amson H E Bourland W A Marchand G R Farley D B & Van Orden D E Furosem de induced release of prostagland n E to increase renal blood flow Proc Soc Exp B ol Med 150 104 1975

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Psychological and Social Problems Encountered in Active Treatment of Chronic Uraemia

III Prediction of the Living Donor s Psychological Reaction

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ACT Sixteen kidney donors were inter by a psychiatrist and given the Rorschach test and one year after operation We used our s study as a basis in predicting the expectable psychic traumatization that the donation pro- ld provoke In 10 of the donors the predic wed to be correct A trend towards a better ability was observed in cases of successful ntation An unsuccessful operation is always d by psychological complications reducing sibilities of an accurate prediction and neces- psychotherapeutic help The present proce- re clinically simple and require relatively little

ds kidney donors psychology of donors d Scand 208 285 1980

In the long-term psychological consequences ey donation 64 volunteer donors were sub- to psychiatric interview and given the ach test at 6 months to 6 years after trans ion. Special attention was paid to how the n process had been experienced and how it eracted in the donor s personality (1)

th s study revealed that donation may in ases have a negative influence on the donor s al y another study on 16 volunteer donors examined before and one year after dona as conducted Our purpose was to clarify to hen it is possible to predict the donor s reaction to the donation i e how dramatic of the transplantation would be

SUBJECTS AND METHODS

purpose every prospective donor in the years was systematically examined by psychological and psychiatric methods as well which here also comprised a psychiatric interview and the Rorschach test

The psychiatric interview lasted regularly for about 45 min This time was divided between two objectives 1) to obtain a fairly accurate global overview on the prospective donor's personality and 2) to assess the important factors concentrating around the donation procedure as such The latter part of the interview was based on previous experience and our earlier studies One year after the transplantation the donor was seen again This time the 45-minute psychiatric interview was dedicated mainly to the examination of the phenomenology of the donor s experiences during the transplantation procedures and the time elapsed after donation

The psychiatric interview was on both occasions supplemented by the Rorschach test. This test one of the most established standard procedures in clinical psychology is well suited to unearthing less conscious intrapsychic processes and thus giving a more deep and broad description of the examinee s psyche when used together with interview data

During the examination period 34 prospective donors were examined for transplantation Sixteen of them became kidney donors because their histocompatibility proved acceptable and none of the other somatic contraindications were demonstrable Of these 4 gave their kidney to their child 10 to their brother or sister one to her grandchild and one to his aunt Transplantation was unsuccessful in four cases One of these recipients died within one month after transplantation On the basis of the examination before transplantation a brief clinical vignette for each of the 16 donors was worked out by a team concentrating especially on the psychodynamic factors which were found significant in our previous report (1) These vignettes were then crystallized into a prediction of how traumatically the donation would be experienced by the donor In accord with our previous report the predictions were classified as 1) no trauma, 2) mild trauma, 3) moderate to severe trauma (Table I)

Each donor was re-examined as accurately at one year after the donation as feasible using the same methods as before donation As previously the team held a conference on each case to assess how traumatic the donation had been

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Skeletal Scintigraphy with Technetium Diphosphonate in Multiple Myeloma– a Comparison with Skeletal X-Ray

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ACT Twenty one patients with multiple a were examined in close time relation with X ray survey and bone scanning using um diphosphonate Results indicate that X- perior to bone scan in detecting myelomatous sions Approximately twice as many lesions tected by X ray as by bone scan An exception general finding is the lumbar spine and rib which the two methods are equally reliable negative bone scan does not exclude the pos of a myelomatous bone lesion

ds bone scanning skeletal scintigraphy skeletal multiple myeloma

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tic lesions are important manifestations of e myeloma The mechanism behind bone de m is unknown but has been ascribed to a e effect of the neoplastic bone marrow cells lves (9) Plain X ray of the skeleton has for ears been a routine procedure in the search bone lesions (13) Radionuclide bone scan ing various technetium isotopes has recently widespread use with the purpose of detect one metastases from various malignant s (1 15 18) Many reports have indicated eletal scintigraphy in this respect is simpler orm and more sensitive than plain skeletal (2 4) Skeletal scintigraphy has been used to bone lesions also in multiple myeloma but sults have been contradictory and seem to e that scintigraphy is less effective in this than skeletal X ray (2 7 16)

therefore found it important to perform a tatic comparative study of the skeletal X ray s and scintigrams in a series of multiple ma patients who had been examined in close lation

PATIENTS AND METHODS

Twenty-one patients with multiple myeloma were studied Diagnostic criteria included numerous lytic bone lesions bone marrow findings with marked increase in plasma cells with malignant characteristics (chromophobe nu cleoli multinucleated cells) and tendency to sheet like growth plasma IgG or IgA M-component and/or urinary M-component Thus two patients had urinary M-compo nents only and together with plasma hypogammaglobu linemia fulfilled the criteria for a diagnosis of light chain disease (19) One patient lacked M-component in plasma and urine and was classified as having non secretory myeloma (11) In addition several patients also had myeloma accompanying features like anemia hypoal buminemia or hypercalcemia

The study was carried out between Oct 1977 and Dec 1978 All patients were admitted to or seen in the Outpa tient Section of the Department of Internal Medicine University Hospital Linköping Sweden Skeletal X ray studies and scintigraphy were performed in the Depart ments of Radiology and Radiophysics Skeletal X ray and scintigraphy were performed at a maximum interval of 30 days In most instances however only a few days elapsed between the two examinations

Skeletal X ray survey included the skull spine (except for the cervical spine) pelvis arms and legs (hands and feet were not included) Radionuclide bone scanning in volved i v injection of 15 mCi technetium ethane 1 hy droxy 1 1-diphosphonate or methylene diphosphonate The entire body of the patient was scanned after 3 hours with a gamma camera (Maxicamera I General Electric)

For the purpose of comparing the effectiveness of the two methods 15 regions of the skeleton were defined as follows 1) Skull 2) thoracic spine 3) lumbar spine 4–5) right and left rib cage 6–7) right and left humerus 8–9) right and left lower arm 10–11) right and left pelvis 12–13) right and left femur 14–15) right and left lower leg The number of positive" (with one or more lesions) regions detected by the two methods were enumerated and sum med up X ray films were reviewed by two radiologists independently

It was registered if a patient had received radiotherapy to a particular region since it has been reported that radiotherapy may influence the result of skeletal scinti graphy by reducing the uptake of the nuclide (5)

RESULTS

In 17 cases examined at an interval of less than 30 days skeletal X ray demonstrated lesions in 101 of 243 regions stud ed while skeletal scintigraphy re vealed only 54 positive of 243 regions stud ed In 4 cases examined at intervals of 2–3 months the figures were 18 positive of 60 regions examined with skeletal X ray and 8 positive of 60 ex amined with skeletal scintigraphy Correction for given radiotherapy d d not influence these results Close correlation between results obtained by the two independent X ray reviewers was noted Thus X ray examination revealed more lytic bone lesions in most regions than scintigraphy However the two methods seemed to be equally effective in re gions involving lumbar spine and rib cage

DISCUSSION

This study shows that skeletal scintigraphy is in ferior to skeletal X ray in detecting bone lesions due to multiple myeloma Approximately twice as many lesions as by scintigraphy were detected by X ray An important conclusion is also that a normal skele tal scintigraphy does not exclude myelomatous skeletal lesions evident on X ray

There seems to be an exception to this general rule In the lumbar spine and the rib cage the two methods of examination are equally effective The reason for this is obscure but may be related to increased occurrence of pathological fractures (or infractions) in these weight bearing and vulnerable regions Fractures and callus formation in them selves cause increased uptake of the isotope and the number of lesions detected by the scintigraphic procedure may be increased (3 12 17) The cause of the decreased sensitivity of skeletal scintigraphy in multiple myeloma as compared to bone metas tases of various mal gnant tumours is not clear at present However the uptake of bone seeking isotopes seems to be related ma nly to osteoblastic processes and neoplasms that metastasize to bone are associated with both osteolytic and osteoblastic activity Multiple myeloma on the other hand is almost always osteolytic with very little new bone formation (13) Also evidence has been presented (14) for the secretion of an osteoclast stimulating factor in myeloma that appears closely related if not identical to osteoclast activating factor that has recently been identified (6 10) Thus extensive osteoclast activity in myeloma may well suppress osteoblastic activ ty and therefore inh bit up take of bone seeking isotopes

REFERENCES

1 Bell E G Blair R J Subramanian G & M J G Evaluat on of 99 m Tc po yphos scann ng for neoplastic skeletal d sease J N 13 413 1972
2 Bell veau R E & Spences R Incidence and bone les ons detected by 99 m Tc-pol ph scans in pat ents w th tumors Cancer 36 3
3 Charkes D N Durant J & Barry W E Bo in mult ple myeloma Arch Intern Med 130 5
4 C trin D L Bessent R G & Greg W comparison of the sens t v ty and accuracy of Tc^{m} phosphate bone scan and skeletal radiog the d agnos s of bone metastases Cl n Radiol 1977
5 Cox P H Abnormal t es in skeletal uptake of polyphosphonate complexes in areas of b soc ated with t ssues which have been sub rad at on therapy *Br J Rad ol 47 851 1974*
6 Horton J E Ra sz L G S mmons H et al resorb ng act v ty in supernatant flu d from human peripheral blood leucocytes Sc ence 1975
7 Hubner K F Andrews G A H Poggenburg J K Jr & Salmon A The earth radionuclides and other bone seeker evaluat on of bone les ons in pat en s w myeloma or sol tary plasmocytoma Rad 125 171 1977
8 Jones S E & Salmon S E The role of cl des in cl n cal oncology Sem n Nucl Med 1976
9 Kobayashi H Potter M & Dunn T B sions produced by transplanted plasma cell BALB/C m ce J Natl Can er Inst 8 649 19
10 Lutsen R A Mundy G R Trummel C L *Partial purificat on of osteoclast ac y fac* phytohemagglut nin st mulated human leuc Cl n Invest 53 1473 1974
11 Manc lla R & Dav s G L Nonsecretory myeloma Am J Med 63 1015 1977
12 Marty R Denney J D McKamey M R ley M J Bone trauma and related ben Assessment by bone scanning Sem n Nucl 6 107 1976
13 Meszaros W The many facets of multiple m Sem n Roentgenol 9 219 1974
14 Mundy G R Ra sz L G Cooper R A ter G F & Salmon S E Ev dence for the of an osteoclast st mulat ng factor in r Engl J Med 291 1041 1974
15 de Nardo G L Jacobsson S I & Ra Sr bone scan n neoplast c d sease Semin N 2 18 1972
16 Patton D P & Woolfenden J M The Rad onucl de bone scanning in diseases of the Rad ol Clin North Am 15 177 1977

~aren J Salokannel J & Timonen T Strontium ~ profile counting of spine in multiple myeloma Blut 351 1974
~ramanian G McAfee J G Blair R J ~ffelz F A & Thomas F D Technetium 99 ~ethylene disphosphonate—superior agent for skeletal imaging comparison with other technetium complexes J Nucl Med 16 744 1975
19 Williams R C Jr Brunning R D & Wollheim F A Light chain disease An abortive variant of multiple myeloma Ann Intern Med 65 471 1966

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Urinary Excretion of Inorganic Sulfate, Ester Sulfate, Total Sulfur and Taurine in Cancer Patients

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[...]ACT The urinary excretion of inorganic sul[...] [e]ster sulfate, taurine and total sulfur has been [...]ed in 18 patients with malignancy, and com[...] [w]ith those of an age-matched reference group [ab]solute amount of inorganic sulfate was sig[...]tly lower in the cancer group, whereas an in[...] [...] ester sulfate excretion was observed Re[...]xcretion of total sulfate (inorganic plus ester [...]) and increased excretion of "neutral sulfur" [...]ulfur minus total sulfate) in the cancer group [...]culated from these data If these values were [...]lated with respect to creatinine, no significant [...]ces were found for inorganic and total sulfate [...] the two patient groups, whereas ester sulfate [...]e 'neutral sulfur' fractions were still in[...]. The enlarged 'neutral sulfur" could to a [...]tent be explained by an increased excretion of [...] The mechanism behind these findings is dis[...]

[...]rds inorganic sulfate neutral sulfur taurine

[...]d Scand 208 ?93 1980

[...] Papadopoulou (10) reported that cancer pa[...] showed a decreased urinary excretion of in[...] and total sulfur and a concomitant increase [...] neutral sulfur fraction She concluded that [...]e of oxidation of sulfur containing amino [a]nd other sulfur compounds found in the [...] sulfur fraction was decreased in cancer pa[...] As no reports confirming or disputing her have appeared in the literature we have [...]ned the present investigation

PATIENTS AND METHODS

[...]cer group consisted of 8 men and 10 women (mean [...] years range 47–80) all with histologically veri[...] [...]cer of d gnity located in the female genital tract [...]h liver lung large bowel breast or kidney One had evide[n]ce of liver metastases but none had any clinical sign of malnutrition Patients treated for minor diseases in the Medical and Orthopedic Departments 7 men and 6 women with a mean age of 66 years (range 55–83) were used as reference group All patients were on a standard hospital diet and had no laboratory sign of kidney dysfunction

All 24 hour urine collections were made with thymol isopropanol as preservative (8) Urine samples were analyzed for total sulfur inorganic sulfate and ester sulfate according to Lundquist et al (7) Total sulfate was calculated as the sum of inorganic and ester sulfate and the neutral sulfur fraction as the difference between total sulfur and total sulfate Taurine was determined according to Sorbo (15) Creatinine analysis was performed according to the standard Jaffe method (2)

RESULTS

The results shown in Table I demonstrate that the excretion of inorganic and total sulfate was decreased but that of ester sulfate somewhat increased in the cancer group Furthermore a significantly increased excretion of neutral sulfur was observed in the cancer patients

We have found that a sex difference exists for the excretion of inorganic sulfate and total sulfur in healthy human subjects (7) This difference disappeared when the values were recalculated relative to creatinine Consequently we recalculated our excretion values for the cancer and reference groups with respect to creatinine excretion As shown in Table I the differences in excretion of inorganic and total sulfate between the two groups were no longer significant whereas the ester sulfate and neutral sulfur excretions were still significantly higher in the cancer than in the reference group

As it is known that certain analgesics are excreted as their sulfate esters (6) we checked that our cancer patients did not receive such compounds The increased ester sulfate excretion is thus unexplained Similarly certain sulfur-contain

Table I *Urinary excretion of sulfur metabolites in cancer patients (mean ± S D)*

Compound	Cancer group		Reference group	
	mmol/24 h	mol S/mol creatinine	mmol/24 h	mol S/mol creatinine
Total sulfur	16 1±7 6	2 06±0 67	19 3±5 0	1 86±0.29
Inorganic sulfate	11 0±6 0*	1 36±0 48	15 7±4 1	1.52±0 28
Ester sulfate	2 30±0 95*	0.32±0 17*	1 16±0 69	0 16±0 05
Total sulfate	13 2±6 5*	1 68±0 56	17 6±4 6	1 72±0.25
Neutral sulfur	3 06±1 8*	0 39±0 17*	1 72±0 86	0 17±0 07
Taurine	1 45±0.33*	0 19±0.062*	0 50±0 23	0 047±0 017

* *Significantly different from the reference group Student s t test ($p<0$ 05)*

ing antibiotics such as penicillin and cephalosporin can be expected to increase the neutral sulfur" fraction However none of our cancer patients received such compounds An important component of the neutral sulfur fraction is taurine (9) The determination of taurine showed that the excretion was significantly higher in cancer patients than in the reference group (Table I) This taurinuria explained at least to a large extent the increased excretion of neutral sulfur" in cancer patients

DISCUSSION

Our results that the absolute amounts of inorganic sulfate found in the urine of cancer patients were lower than the excretion in the control group agree with the results of Papadopoulou (10) However her conclusion that cancer patients have an impaired ability to oxidize sulfur amino acids to sulfate appears unlikely as we found that the excretion of inorganic sulfate was not significantly different from that of the cancer patients when related to creatinine excretion It should be noted that all our patients had normal serum creatinine values in accordance with a normal kidney function

We found an increased excretion of ester sulfate in the group of cancer patients The same conclusion could be drawn from the data presented by Papadopoulou (10) Raised amounts of ester sulfate appear in the urine from an increased production of phenols by bacterial degradation of aromatic amino acids (tryptophan tyrosine and phenylalanine) in the bowels (1) By this mechanism patients suffering from constipation show increased excretion of ester sulfate (3) Obstipation cannot be excluded as a cause of the increased excretion of ester sulfate in our cancer patient group

A noteworthy finding was an increased taurine excretion in the cancer group Taurine is one most abundant amino acids normally found [illegible] Taurine is synthesized from cysteine in th[illegible] and possibly other tissues (5) and is mainly [illegible] to the intracellular compartment A high con[illegible] tion of taurine is found in many tissues e g [illegible] striated muscle brain trombocytes and le[illegible] In some of these tissues the concentration of [illegible] is 10 times higher than any other amino acid [illegible] Taurine is mainly eliminated via the kidney [illegible] the daily excretion represents only a few pe[illegible] the total body taurine (17) One important [illegible] of taurine is bile acid conjugation as one [illegible] the bile acids are conjugated with taurine [illegible] creasing evidence that taurine is function[illegible] neurotransmitter or neuromodulator in [illegible] retina has been presented recently (18) [illegible] more taurine plays a role in the regula[illegible] membrane excitability in the heart and the [illegible] increased ventricular concentration of tau[illegible] congestive heart failure (4)

Taurinuria observed in our cancer patients [illegible] our knowledge not been reported in the lit[illegible] An increased taurine excretion occurs a[illegible] body irradiation (5) and cytostatics (13) b[illegible] our patients received such treatment As [illegible] centrations of taurine are present in many [illegible] cell damage will induce an increased taurine [illegible] centration in plasma and as that taurine has [illegible] renal clearance (16) it is rapidly excreted [illegible] urine A number of pathological conditions [illegible] cellular damage have been reported to [illegible] taurinuria (5 11) Consequently the [illegible] taurine excretion found in cancer patients [illegible] not be regarded as a specific sign of cancer [illegible] non specific response to cellular damage [illegible] be noted that the taurinuria observed by [illegible] the same order of magnitude in the different [illegible] of cancer studied The number of patients

r small and the results should be inter
tiously

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REFERENCES

ce I & Schoosby H Value of urinary sum
nol and indican determinations in the diagnosis
tagnant loop syndrome Scand J Gastroenterol
1976

n A L. Grady H J & Stanley M A
ination of creatinine by means of automatic
al analysis Am J Clin Pathol 35 83 1961

ngs J H Hill M J Bone E S Branch W
nkins D J A The effect of meal protein and
fiber on colonic function and metabolism Am
Nutr 3? 2094 1979

le R Metabolism and function of taurine in
rt In Taurine (ed R Huxtable and A Bar
p 99 Raven Press New York 1976

m J G & Smith L H Jr Biochemistry
ysiology of taurine and taurine derivates
Rev 48 424 1968

G & Yamada H Drug biotransformation in
ns in man III Acetaminofen and salicyl
I Pharm Sci 60 215 1971

ist P Mårtensson J Sorbo B & Öhman
S Turbidimetric methods for the determinations of inorganic sulfate ester sulfate and total sulfur in urine Clin Chem In press 1980

8 Naftalin L & Mitchell I R A new urine preservative Clin Chim Acta 3 197 1958

9 Nöcker J Die klinische Bedeutung der Schwefelfraktionen im Urin Dtsch Arch Klin Med 202 527 1955

10 Papadopoulou D Urinary sulfur partition in normal man and in cancer patients Clin Chem 3 257 1957

11 Rylance H J & Myhal D R Taurine excretion and the influence of drugs Clin Chim Acta 35 159 1971

12 Schrier B K & Thomson E J The role of glial cells in the mammalian nervous system J Biol Chem 249 1769 1974

13 Schubert J & Sorbo B The effect of alkylating agents on the excretion of taurine in the urine of rats Experientia 19 105 1963

14 Sjovall J Bile acids in man under normal and pathological conditions Bile acids and steroids 73 Clin Chim Acta 5 33 1960

15 Sorbo B A method for determination of taurine in urine Clin Chim Acta 6 87 1961

16 Soupart P Free amino acids of blood and urine in the human In Amino acid pools Distribution formation and function of free amino acids (ed J T Holden) p 220 Elsevier Amsterdam London and New York 1962

17 Sturman J A Gershon W H Hofmann A F & Thomas P J Taurine pool size in man Studies with ^{35}S taurine In Taurine (ed R Huxtable and A Barbeau) p 21 Raven Press New York 1976

18 Sturman J A Rassin D K & Gaulle G E Taurine in development Life Sci 21 1 1977

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Blood Glucose Control and Lipolysis in Diabetes Mellitus

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RACT The relationship between the blood level and the rate of lipolysis was investigated maturity onset diabetics (MOD) and 9 juvenile diabetics (JOD) Subcutaneous adipose tissue incubated with and without isoprenaline or noradrenaline Before antidiabetic treatment the blood concentration was positively correlated with and catecholamine-induced rates of lipolysis in (R=0 41–0 60) and in JOD (r=0 51–0 71) duction in blood glucose concentration during antidiabetic treatment was positively correlated with reduction in the rate of lipolysis in MOD 0–0 64) and in JOD (r=0 75–0 90) Fat cell and blood glucose level were not correlated either treated or treated diabetics In diabetes mellitus blood glucose homeostasis and rate of lipolysis adipose tissue seem to be associated The relation most apparent in JOD

words diabetes mellitus adipose tissue lipolysis
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accelerated rate of lipolysis in adipose tissue in diabetes mellitus (2–5 8 12) is of considerable clinical significance since it may be a contributory factor to several complications of diabetes mellitus The purpose of the present study was to ascertain whether in diabetes mellitus the rate of lipolysis is related to the blood glucose control Basal and catecholamine induced glycerol release in vitro was determined in fragments of subcutaneous adipose tissue from untreated patients with maturity onset (MOD) and juvenile onset (JOD) diabetes The effect that antidiabetic treatment exerts on lipolysis and blood glucose was also investigated

STUDY POPULATION

The diabetics consisted of inpatients with recently diagnosed diabetes 9 with JOD and 19 with MOD They were otherwise healthy and no selection on the basis of sex was made A subcutaneous fat biopsy was taken from the femoral region after an overnight fast At this time no antidiabetic treatment had been received Twenty-one patients were re-examined during antidiabetic therapy for at least 3 months This consisted of diet alone or administration of sulphonylurea in MOD (16 patients) and insulin in JOD (5 patients) The patients were re admitted to hospital and subcutaneous fat specimens were taken from the contralateral region after an overnight fast before administration of insulin or sulphonylurea At this time four JOD patients and one MOD patient had glucosuria (less than 200 mmol/24 h) None had ketonuria

The investigation was approved by the Ethical Committee of the Karolinska Institute Details of the study were explained to the patients and their consent was obtained

METHODS

Local anaesthesia was induced with prilocaine chloride as described previously (2) The blood glucose concentration was measured (7) on 3 or 4 occasions during 12 hours before and after the biopsy A mean blood glucose concentration was calculated from these values and the fasting value

Adipose tissue was divided into 50 mg segments and preincubated for 30 min in Krebs Henseleit bicarbonate buffer (37°C pH 7 4) containing 40 mg/ml of dialyzed bovine serum albumin (Armour Fraction V England) Then adipose tissue 100 mg was incubated for 2 hours in 1 ml of fresh buffer of the same type and two aliquots of the medium were removed for glycerol estimation (6) All incubations were done in triplicate or quadruplicate with air as the gas phase

The fat cell diameter was determined by the method of Sjostrom et al (13) Fat cell volume and fat cell number were calculated by the method of Hirsch and Gallian (9)

Noradrenaline bitartrate (Astra Sweden) and isoprenaline hydrochloride (Winthrop England) were added to

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Abbreviations MOD = maturity onset diabetes (diabetics) *JOD = juvenile onset diabetes (diabetics)*

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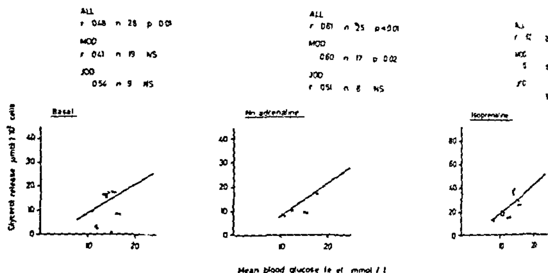


Fig 1 Correlation between mean blood glucose level and rate of lipolysis in untreated diabetics Adipose tissue was incubated in the absence and presence of noradrenaline or isoprenaline The mean blood glucose level was deter mined and compared with the rate of glycerol rel vitro using linear regression analys s x=y MOD The regression line represents the whole

the medium in vitro to give a final concentration of 6 μmol/l the level known to furnish the maximum effect (3) Linear regression was examined by the method of least squares

RESULTS

In the whole material before treatment for diabetes mellitus there was a significant positive correlation between the mean blood glucose concentration and the rate of glycerol release in vitro both in the presence and absence of catecholamines When the patient group was divided into MOD the values for the correlation coef were in general higher in JOD (0 51–0 71 MOD (0 41–0 60) The fasting blood gl and the rate of lipolysis were also significan related in the whole patient series (data not

In the patients who were re-examined a tidiabetic therapy the decrease in fasting bl cose concentration was positively and signif

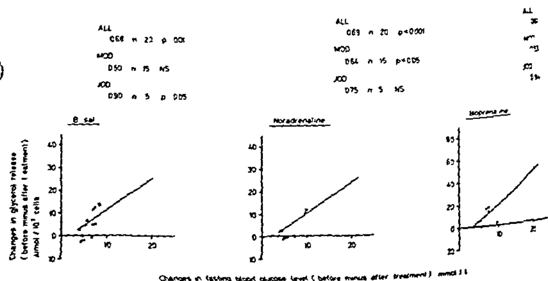


Fig 2 Influence of antidiabetic therapy on the relation ship between fasting blood glucose level and rate of lipolysis For further details see legend to Fig 1

ed with the decrease in the basal and lamine stimulated rates of lipolysis (Fig 2) values for the correlation coefficients were d in JOD (r=0 75–0 90) than in MOD –0 64) In the whole material the decrease t blood glucose level was also significantly ed with the decrease in the rate of lipolysis ot shown)

was no correlation between fat cell size od glucose concentration

DISCUSSION

mobilization from the fat depots is known to nced in JOD and MOD (3–5 8 12) Al it decreases during antidiabetic therapy (4 s been found both in vivo (11) and in vitro f polysis is enhanced also when the disease n brought under control This suggests that ons in lipolysis and glucose homeostasis are ciated in diabetes mellitus In the present however there was a positive correlation n the plasma glucose level and the lipolytic in adipose tissue before treatment as well cholamine-stimulated as for unstimulated lipolysis Furthermore when hypergly was brought under control the reduction blood glucose level and the decrease in the lipolysis were correlated This is observed JOD and MOD but the relationship appears rmer in JOD The correlation between the lucose level and the rate of lipolysis strongly s that the homeostatic mechanisms that glucose utilization and free fatty acid mobili in diabetes mellitus are interrelated at least

mechanisms behind the link between blood control and lipolysis are not known The nous insulin level or different degrees of in sistance are probably not the main factors sible for the relationship If so one would a better correlation in MOD than in JOD If ig the opposite phenomenon was observed present study Neither is it probable that the nship is solely conditioned by the action of nous catecholamines since maximal effec ncentrations of catecholamines were used in t has also been suggested that the fat cell size is a factor in the control of metabolism in diabetes (10) In the present investigation however fat cell size was not correlated with the blood glucose level

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REFERENCES

1 Arner P Relationship between intracellular cyclic AMP and lipolysis in human adipose tissue Acta Med Scand 200 179 1976
2 Arner P Arner O & Östman J The effect of local anaesthetic agents on lipolysis by human adipose tissue Life Sci 13 161 1973
3 Arner P Engfeldt P & Östman I Relationship between lipolysis cyclic AMP and fat-cell size in human adipose tissue during fasting and in diabetes mellitus Metabolism 28 198 1979
4 Arner P & Östman J Abnormalities in the adrenergic control and the rate of lipolysis in isolated human subcutaneous adipose tissue in diabetes mellitus Diabetologia 12 593 1976
5 Bjorntorp P & Hood B Studies on adipose tissue from obese patients with or without diabetes mellitus I Release of glycerol and free fatty acids Acta Med Scand 179 221 1966
6 Chernick S S Determination of glycerol in acylglycerols Methods Enzymol 4 627 1969
7 Coburn H J & Caroll J J Improved manual and automated colorimetric determination of serum glucose with use of hexokinase and glucose-6-phosphate dehydrogenase Clin Chem 19 127 1973
8 Ginsberg Fellner F & Knittle J I Adipose tissue cellularity and metabolism in newly diagnosed juvenile diabetics Diabetes 22 528 1973
9 Hirsch J & Gallian E Methods for the determination of adipose cell size and cell number in man and animals J Lipid Res 9 110 1968
10 Langer L Lindholm B Örndahl G & Bjorntorp P Adipose tissue cellularity in relation to metabolism in juvenile onset diabetes mellitus Diabetologia 11 101 1975
11 Nordllander S Östman J Cerasi E Luft R & Ekelund L G Occurrence of diabetic type of plasma FFA and glycerol response to physical exercise in prediabetic subjects Acta Med Scand 193 9 1973
12 Östman J Studies in vitro on fatty acid metabolism of human subcutaneous adipose tissue in diabetes mellitus Acta Med Scand 177 639 1965
13 Sjostrom L Bjorntorp P & Vrána J Microscopic fat cell size measurements on frozen-cut adipose tissue in comparison with automatic determinations of osmium fixed fat cells J Lipid Res 12 521 1971

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Comparative Single-Dose Kinetics and Effects of Four Sulfonylureas in Healthy Volunteers

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ACT The single dose kinetics and effects of mide (500 mg) chlorpropamide (250 mg), lamide (5 mg) and glipizide (5 mg) were com 7 healthy male volunteers by measurements n concentrations of the drugs and of plasma and blood glucose The drugs were adminis- th on an empty stomach and together with a dized breakfast The concentrations of tol le and chlorpropamide were measured by gas tography, those of glipizide with high pres- uid chromatography, those of glibenclamide ulin by radioimmunoassay and those of glu the hexokinase method Glipizide and gliben were more potent inducers of insulin re d blood glucose reduction than tolbutamide lorpropamide As the concentrations of the two drugs were in the range of nmol/l and f the latter two in the μmol/l range the find pport the notion that the intrinsic activity of second-generation sulfonylureas is at least mes greater than that of the two first genera gs. Glipizide seemed to be a more potent and apid insulin releaser than glibenclamide but y be secondary to biopharmaceutic differences the two preparations The bioavailability of le was apparently greater than that of gliben Both glibenclamide ($t_{\frac{1}{2}}$=1 8 h) and glipi ($t_{\frac{1}{2}}$=4.3 h) showed much shorter elimination es than tolbutamide (7 h) and chlorprop (34 h) It seems probable, however, that alf lives are not fully informative as to the n of action of the drugs

rds sulfonylureas kinetics effects

d Scand 208 301 1980

nt 10-year follow up indicates that impaired tolerance if left untreated carries a great development into manifest diabetes but that velopment can be prevented or postponed by nation of diet regulation and tolbutamide (12) Another analysis of the same material has shown that this medication reduces rather than enhances cardiovascular morbidity (8) These findings suggest that sulfonylurea drugs are beneficial rather than harmful and this has reawakened interest in the search for an optimal sulfonylurea preparation

The aim of sulfonylurea treatment is normalization of glucose economy In particular it is important to enhance the disposition of the large carbohydrate loads that follow each meal On the other hand the sulfonylurea effect should not prevail between meals and the drug should not be liable to provoke long lasting hypoglycemia Accordingly the sulfonylurea should be as potent rapid acting and short acting as possible In an attempt to compare these capacities of tolbutamide chlorpropamide glibenclamide and glipizide single standard doses of these drugs were given both with and without a standardized breakfast to seven healthy volunteers The effects on plasma insulin and blood glucose were recorded together with the concentration profiles of each drug

SUBJECTS

Seven male volunteers participated in the study They were considered healthy as judged by conventional physical examinations and routine blood tests Their mean ages and ideal body weights were 26 2 (± S D 1 9) years (range 23 5–29) and 96 8 (± S D 5 0)% (range 90 1–101 4) Each subject was extensively informed and gave written consent

METHODS

Protocol

On 9 different mornings at intervals of at least one week the subjects came to the laboratory after a 10 h fast (10

Abbreviations $t_{\frac{1}{2}}$=half life AUC area under the curve

p m –8 a m) All underwent each of the following treatments 1) A standardized breakfast meal without drug intake 2–5) meal plus 500 mg tolbutamide (Artosin* Boehringer Mannheim Mannheim Federal Republic of Germany) 250 mg chlorpropamide (Diabines(e)* Pfizer Groton Conn USA) 5 mg glibenclamide (Daonil* Hoechst Frankfurt Federal Republic of Germany) or 5 mg glipizide (Min(i)diab* Carlo Erba Milan Italy) 6–9) the same drugs without meal (fasting continued for another 4 h) The standardized meal consisted of 400 ml low fat milk 20 g white bread with 5 g butter and 35 g cheese and 150 ml non sweetened black coffee yielding a total energy of 430 kcal or 1 800 kJ

Analyses

Serial blood samples were drawn via an indwelling antebrachial venous polyethene catheter Blood glucose and plasma insulin were followed for 3 h Blood glucose concentrations were determined by the hexokinase method (4) and plasma insulin concentrations were measured by a commercial solid phase radioimmunoassay (Phadebas Insulin Test* Pharmacia Uppsala Sweden) The serum concentrations of the drugs were monitored for 24–48 h Tolbutamide and chlorpropamide were determined by gas chromatography (11) The possibility of chromatographic pyrolysis of sulfonylurea was avoided by using an all glass system and a low injection temperature The interassay variability was 5 1% (S D of a serum pool value) Glipizide was measured by a high pressure liquid chromatographic assay with a sensitivity of 20 nmol/l and an interassay variability of 6 2% (15) Glibenclamide was determined by radioimmunoassay (7) The antibody reacts not only with glibenclamide but also with its hydroxylated active metabolite However as the metabolite is normally present only in minute amounts and has a very short half life ($t_{½}$) (14) its interference would be negligible in a single-dose study on healthy volunteers The assay sensitivity was 20 nmol/l and the interassay variation 9 9%

Calculations

The serum concentrations of the four drugs were plotted against time Peak concentration was defined as the highest values recorded As the absorption and elimination phases could not be safely distinguished from each other no calculations were carried out as to absorption kinetics The elimination $t_{½}$ was calculated by regression analysis The area under the curve (AUC) was estimated by the trapezoidal rule The statistical significance of differences was calculated by Student s paired t tests on intraindividual data pairs and by Wilcoxon s signed rank test

RESULTS

Drug concentrations in serum

Fig 1 shows the single dose kinetics of tolbutamide (500 mg) chlorpropamide (250 mg) glibenclamide (5 mg) and glipizide (5 mg) ingested in the fasting state The kinetic data under fasting and non fasting conditions are given in Table I It can be seen that the former two drugs yielded serum concentrations of several μmol/l while those of the latter tw in the nmol/l range The elimination of propamide (mean of 34 h in the fasting st much slower than that of tolbutamide ($t_{½}$ 0 001) which in turn was slower (p<0 01) t of glipizide (4 3 h) and glibenclamide wh shortest of all (1 8 h p<0 05 vs glipizide $t_{½}$ figures were recorded when the drugs we in the non fasting state (Table I)

Both in the fasting and non fasting s mean peak concentration of glipizide was cally but not significantly higher than glibenclamide A significant difference corded with respect to the time to reach pe centration in the fasting state the mean t h for glipizide while that of glibenclamide (p<0 05) The mean AUC of glibencla smaller than that of glipizide both in the fa non fasting state the latter but not the fo ference reached statistical significance (p<

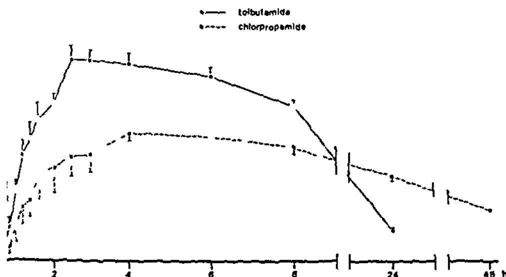
Plasma insulin

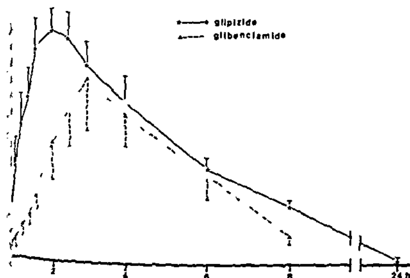
Fig 2 demonstrates the plasma insulin pro lowing intake of the four drugs in the fast The pre exposure mean values did not d nificantly Glipizide promoted an increase insulin that was significantly (p<0 05) ab trol at 45 60 and 75 min after drug int increments seen after administration o clamide and tolbutamide did not reach significance Chlorpropamide evoked h change at all

Table II shows the plasma insulin levels intake of the four drugs both with and standardized breakfast The pre-exposu did not differ significantly Both glipiz glibenclamide yielded greater plasma insul ments than did the meal only However s significance was reached only for glibencla 90, 120 and 150 min (p<0 05) No signifi ference was recorded at any interval betw plasma insulin concentrations following plus meal and glibenclamide plus meal

Blood glucose

The blood glucose profiles following int four drugs in the fasting state are shown Significant reductions (p<0 05) of the bl cose concentrations were recorded at 45 a (tolbutamide and glipizide) at 75 90 12 min (tolbutamide glipizide and glibencla





Single-dose kinetics of (*a*) tolbutamide (500 mg) chlorpropamide (250 mg) and (*b*) glibenclamide (5 mg) glipizide (5 mg) in seven healthy volunteers following intake on an empty stomach The calculated kinetic data are given in Table I

...tion (glipizide and glibenclamide) The mean ...al blood glucose reduction after chlor... ...de did not reach statistical significance at ...rval studied Glipizide seemed to evoke a ... and more rapid glucose diminution than ...amide but the difference did not reach ...l significance at any interval studied Both these drugs on the other hand evoked glucose reductions that were significantly ($p<0.05$) more marked than those following tolbutamide at 60 75 90 (glipizide) 120 and 180 min (glipizide and glibenclamide)

Concurrent administration of drugs and meal (Table III) yielded smaller blood glucose incre...

Table I *Pharmacokinetic parameters of four sulfonylureas in seven healthy volunteers follow[illegible] oral dose ingested both on an empty stomach and with a standardized breakfast (mean ±S E M [illegible] parentheses)*

C_{max}=peak concentration t_{max}=time to peak concentration

	Tolbutamide (500 mg)	Chlorpropamide (250 mg)	Glibenclamide (5 mg)	Glipizide (5 mg)
Fasting				
C_{max} (µmol/l)	153±8 (122–178)	100±4 (87–112)	0 592±0 129 (0 231–1 182)	0 703±0 076 (0 346–0 916)
t_{max} (h)	3 4±0 3 (2 5–4 1)	3 2±0 6 (1 5–5 5)	3 4±0 5 (2 5–6)	2 1±0 2 (1.5–2 5)
$t_{½}$ (h)	7 2±0 3 (6 1–8 0)	34±3 (21–43)	1 8±0 3 (1 1–2 8)	4 3±0 7 (2 5–7 3)
AUC (µmol×h×l⁻¹)	1976±76[a] (1587±2180)	2806±157[b] (2121±3317)	2 109±0 411[c] (0 706–3 727)	2 963±0 3 (1 764–4 385)
Non fasting				
C_{max} (µmol/l)	150±9 (122–192)	86±5 (65–101)	0 591±0 049 (0 453–0 868)	0 717±0 059 (0 496–0 884)
t_{max} (h)	4 0±8 (1 5–7 9)	5 4±0 8 (1 3–8 2)	2 6±0 3 (2–4)	2 4±0 2 (1.5–3 0)
$t_{½}$ (h)	7 0±0 3 (5 4–7 9)	40±4 (26–56)	1 6±0 1 (1 2–1 8)	3 9±0 6 (2 0–5 7)
AUC (µmol×h×l⁻¹)	1825±77 (1571–2152)	2728±190[b] (1997–3295)	2 261±0 233 (1 920–2 299)	2 957±0 111[c] (2 560–3 343)

[a] 0–24 h [b] 0–48 h [c] 0–8 h

ments than did the meal only Significance ($p<$ 0 05) was reached both with glipizide (at 75–180 min) and glibenclamide (at 150 min)

DISCUSSION

The kinetic characteristics of sulfonylureas have been described previously (1 16) and the observations made in the present study are [illegible] agreement therewith However there [illegible] few studies concerning the comparati[illegible] and this was the major concern of the [illegible]vestigation Particular emphasis was la[illegible] ences in intrinsic activity and in rapidi[illegible]

The drug measurements showed that

Table II *Plasma insulin levels in seven healthy volunteers following a single oral dose inges[illegible] empty stomach and with a standardized breakfast (mean ±S E M)*

A=500 mg tolbutamide B=250 mg chlorpropamide C=5 mg glibenclamide D=5 mg glipizide

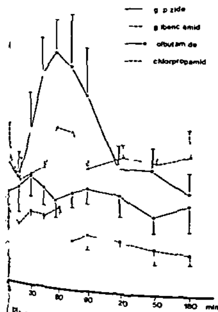
	Time after intake of drug and/or meal (min)								
	0	15	30	45	60	75	90	120	150
A	8±1	9±2	10±2	9±2	8±2	9±2	9±1	9±2	7±[illegible]
B	6±2	5±2	7±2	6±2	7±2	4±1	5+1	5±1	4±1
C	11±3	9±2	10±2	11±2	14±4	14±3	11±2	12±1	[illegible]
D	11±3	10±2	14±3	19±3	21±3	20±4	17+4	11±2	11±[illegible]
Meal only	11±3	24±6	35±3	31±1	30±4	30±4	22±2	17±3	13±3
Meal+A	13±3	31±4	41±5	39±9	25±5	25±5	22±5	18±3	14±3
Meal+B	5±1	27±5	26±4	18±2	16±4	13±2	10±2	9±2	6±[illegible]
Meal+C	11±3	33±7	40±4	38±7	40±3	45±9	43±5	32±5	22±6
Meal+D	15±3	35±8	49±4	41±4	41±5	30±3	31±9	30±6	23±3

II B od glucos levels i i seven healthy v l nteers follo ng a single oral d se ingested both on a i y mach and tl a st ndard ed breakfast (mean±S E M)

mg tolbutam de B 250 mg chlorpropam de C 5 mg gl benclam de D 5 mg gl pizide

	Time after ntake of drug and/or meal (m n)									
	0	*15*	*30*	*45*	*60*	*75*	*90*	*120*	*150*	*180*
	41+01	41+01	39+02	38+01	36+02	36+01	36+02	35+01	34+03	38+01
	44+02	45+02	46+02	44+01	43+01	42+02	42+01	41+01	42+02	45+02
	46 02	44+02	42+03	41+02	39+02	36+03	34+02	32+02	33+02	33+02
	40+02	41+03	38+03	34+02	28+02	23+02	25+02	28±02	30+02	33+01
b)	43 02	46+02	55+02	50+04	44+03	38+02	39+02	40+02	41+01	42+01
	41+01	*44 02*	*50+03*	*44+03*	*34+02*	*33+02*	*31+02*	*36+02*	*37+02*	*40+02*
	46+01	51+02	49+04	44±03	41+03	39+02	40+02	4.3+02	43+01	50+03
	42 02	5.2+02	59+05	49+06	40+05	33±03	32+03	30+02	32+01	3.5+01
)	41+01	49+02	50+03	40+04	27+05	25±03	28+03	27+01	3.5+01	33+03

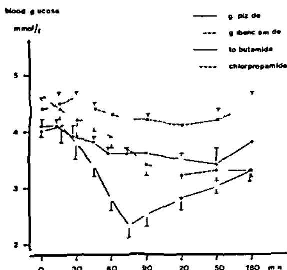
trations of gl p zide and gl benclamide were range of nmol/l while those of tolbutamide lorpropam de were in the μmol/l range As pizide and gl benclamide were at least as e as the two other drugs (vide infra) the s support the not on that the intrins c activity two second-generat on sulfonylureas is at 000 times greater than that of the two first tion drugs



Pla ma in ul n concentrat ons in seven healthy ers following intake on an empty stomach of tol ide (500 mg) chlorp opam de (250 mg) gl ben e (5 mg) and gl p z de (5 mg) The correspond res are gi en in Table II

As far as the difference between glipizide and gl benclamide is concerned it was seen that glipi z de in the fasting state induced a more pronounced increase in plasma insul n than gl ben clamide Moreover glipiz de seemed to promote the greatest blood glucose reduction Further more hypoglycem c reactions were reported by five subjects after gl pizide but by only two after gl benclamide

These find ngs could sign fy that gl pizide is a more potent insul n releaser than glibenclamide However the seem ngly stronger effect of glipiz de



F g 3 Blood glucose concentrat ons n seven healthy volunteers following ntake on an empty stomach of tol butam de (500 mg) chlorpropam de (250 mg) gl ben clam de (5 mg) and gl p z de (5 mg) The correspond ing f gures are g ven n Table III

may be secondary to biopharmaceutic differences between Min(i)diab® and Daonil® tablets in the same dosage at least 40% more glipizide than glibenclamide reached systemic circulation even though the molecular weights differ by only 10% (446 and 494 respectively) Thus it seems probable that the bioavailability of glipizide from Min(i)diab is greater than that of glibenclamide from currently available Daonil Accordingly, the question whether glipizide and glibenclamide differ in intrinsic activity remains unanswered by the present study Another complication in the comparison between the two drugs is that concomitant food intake reduces the absorption rate and hence the effect of glipizide (15) while no such influence has been recorded for glibenclamide (11) A similar tendency was seen in the present study, although the difference did not reach statistical significance

Another finding that may relate to biopharmaceutic differences concerns the rapidity of effect Glipizide seemed to be more rapidly absorbed than glibenclamide and the time to reach peak concentration was significantly longer for glibenclamide (3 5 h) than for glipizide (2 h) even though the peak concentration was higher for the latter than for the former Thus it is likely that glipizide reached its minimum effective concentration more rapidly than glibenclamide This may explain both the impression that glipizide yielded a more rapid effect and the apparently higher potency of this drug (vide supra) Similarly the slight (tolbutamide) or virtually absent (chlorpropamide) effect of the two first generation sulfonylureas may be due not only to their weaker intrinsic activity but also to slower absorption compared to the second generation drugs

The present findings confirm that of the four drugs studied chlorpropamide has the by far longest elimination $t_{\frac{1}{2}}$ exceeding 24 h in each subject with a (fasting) mean of 34 h (16) In addition, the estimated $t_{\frac{1}{2}}$ of tolbutamide about 7 h (16) was much longer than those of glipizide and glibenclamide Furthermore the latter displayed the shortest elimination $t_{\frac{1}{2}}$ of the four drugs with a mean of only 1 8 h (fasting) compared to 4 3 h for glipizide Assuming that the duration of action of each sulfonylurea is related to its plasma elimination $t_{\frac{1}{2}}$ chlorpropamide would be the most long acting one and glibenclamide the one with the shortest duration of action The latter assumption is supported by recent studies suggesting that while the therapeutic effect of glipizide can be [illegible] when this drug is given once daily (5 7), the [illegible] of glibenclamide is reduced when given once [illegible] as compared to the effect of administra[illegible] daily (5) On the other hand the concept of [illegible] clamide as a short acting sulfonylurea [illegible] tradicted by much evidence (9) and by the [illegible] spread clinical experience that glibencl[illegible] provoke long lasting hypoglycemia (? 4)

The apparent contradiction between th[illegible] short $t_{\frac{1}{2}}$ and the allegedly long effect d[illegible] glibenclamide may have several explanations [illegible] ly it is possible that the sensitivity of the [illegible] employed methods is not sufficient to all[illegible] rate determinations of the true elimination [illegible] of glibenclamide and glipizide Indeed stu[illegible] which [14]C labelled drugs have been used [illegible] that both drugs penetrate a deep [illegible] which they are only slowly eliminated (I) [illegible] be excluded moreover, that although the [illegible] metabolite of glibenclamide has a very sho[illegible] healthy subjects (13) it may accumulat[illegible] with impaired renal function and hence p[illegible] effect

To summarize Despite the limited possi[illegible] draw clinically pertinent conclusions from [illegible] dose studies in healthy volunteers the fi[illegible] support the concept that glipizide and glibencl[illegible] are much more potent sulfonylureas than [illegible] tamide and chlorpropamide and that this [illegible] to a major difference in intrinsic activity G[illegible] appears to be more potent and rapid acting [illegible] glibenclamide but this may simply be due to [illegible] ences in the biopharmaceutics of Min(i)di[illegible] Daonil tablets Both glibenclamide and g[illegible] seem to have short elimination half lives [illegible] are probably not informative as regards the d[illegible] of action of these drugs

ACKNOWLEDGEMENTS

This study was supported by grant no [illegible] Swedish Medical Research Council and by a g[illegible] the Swedish Board of Health and Welfare [illegible] Project)

REFERENCES

1 Balant L Fabre J & Zahnd G R Com[illegible] the pharmacokinetics of glipizide and glibencla[illegible] man Eur J Clin Pharmacol 8 63 1975
2 Clarke B F & Campbell I W Long term [illegible]

al of glibenclamide and chlorpropamide in ed maturity-onset diabetics Lancet 1 246

H J & Carrol J J Improved manual and ted colorimetric determination of serum glu ith use of hexokinase and glucose 6-phosphate ogenase Clin Chem 19 127 1973

in C Delporte M P Thomas M & Per d Les accidents hypoglycémiques des thé ques orales du diabète Nouv Presse Med 976

L & Harno K The diurnal pattern of blood and plasma insulin during glibenclamide and e treatment in elderly diabetics Acta Endo- Suppl) 227 1979

V E & Schmidt F M Radioimmuno- : Bestimmung von Glibenklamid Abstract gress der deutschen Diabetes Gesellschaft en 1973

J Jansson B & Weiner L Relationship therapeutic effect and bioavailability of in maturity-onset diabetes mellitus (ab- Excerpta Medica Int Congr Ser 481 1979

G Cardiovascular complications in diabet subjects with reduced glucose tolerance Acta and (Suppl) 605 1977

E F Sulfonylureas Newer aspects of cology and clinical efficacy In Diabetes (ed Malaisse and J Pirart) p 563 Excerpta Medica

10 Prescott L F & Redman D R Gas liquid chromatographic estimation of tolbutamide and chlorpropamide in plasma J Pharm Pharmacol 24 713 1972

11 Sartor G Melander A Schersten B & Wåhlin Boll E Serum glibenclamide in diabetic patients and influence of food on the kinetics and effects of glibenclamide Diabetologia 18 17 1980

12 Sartor G Schersten B Carlstrom S Melander A Nordén Å & Persson G Ten year follow up of subjects with impaired glucose tolerance Prevention of diabetes by tolbutamide and diet regulation Diabetes 29 41 1980

13 Schmidt F H Plasma levels and excretion of glibenclamide in renal insufficiency Atti delle giornale di diabetologia del Mediterraneo pp 1–18 Boehringer Biochem s r l Milano 1975

14 Wåhlin Boll E & Melander A High pressure liquid chromatographic determination of glipizide and some other sulfonylurea drugs in serum J Chromatogr 164 541 1979

15 Wåhlin Boll E Melander A Sartor G & Scherstén B Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects Eur J Clin Pharmacol In press 1980

16 West K M & Johnson P C The comparative pharmacology of tolbutamide carbutamide chlorpropamide and metahexamide in man Metabolism 3 596 1959

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Early Insulin Response in Latent Gestational Diabetes

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RACT *The intravenous glucose tolerance and* **e-stimulated early insulin response (EIR) were d in late pregnancy and post partum in a refer R) group of 9 women and in 18 women with gestational diabetes (LD), defined as a k value 66/h and a normal fasting blood glucose con tion During pregnancy, the LD group showed EIR than the R group However the response between normal and non detectable In the egnant state the EIR was the same in the two The inability to increase the EIR during ncy was most evident in women who even post had an abnormal glucose tolerance In some in the LD group, the EIR during pregnancy en lower than in the non pregnant state The ude of the response in the non pregnant state decisive of the capacity to increase the secre ring pregnancy None of the women in the LD developed manifest diabetes during pregnancy ave birth to children with** *normal birth weight* **neonatal problems were registered except for ild with congenital heart malformation**

rds intravenous glucose tolerance test early insu or e pregnancy gestational diabetes

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nd delayed glucose stimulated early insulin se (EIR) has been considered a characteristic r all stages of the diabetic syndrome includ prediabetic state and has been suggested to rerequisite for the development of manifest s (3) This hypothesis has not been generally ed however (1 14 16 23 24) Pregnancy diabetogenic effect on the glucose tolerance due to a decreased peripheral insulin sen (6 17 25) An inability to increase the insu retion will lead to an impaired glucose toler even initiate manifest diabetes during preg Insulin secretion studies in women with ges l diabetes during and after pregnancy will thus give an opportunity to get further information on the validity of the low insulin response hypothesis

STUDY POPULATION

Gestational diabetes

Pregnant women with glucosuria during the current pregnancy a close relative with diabetes or an abnormal obstetrical history in a previous pregnancy were screened for gestational diabetes by means of their fasting blood glucose concentrations Only women with a relative body mass just before pregnancy of <120% were included If two consecutive fasting blood glucose values in late pregnancy were ≥5 0 mmol/l the woman was subjected to an intravenous glucose tolerance test (IVGTT) including EIR measurement If the fasting blood glucose concentration was <7 2 mmol/l and the elimination of glucose (k value) <0 66/h (<1 10%/min) the woman was considered to have a latent form of gestational diabetes (LD) and was included in the LD group of this study

This selection procedure gave 16 women Two women from the reference (R) group (see below) were added to the LD group as they turned out to have subnormal k values The LD group thus consisted of 18 women aged 20-39 years (median 28) The body mass just before pregnancy was 44-76 kg (median 65) and relative body mass 71-117% (median 101) The body mass gain during pregnancy was 5-30 kg (median 12) The LD group was divided into two equal subgroups on the basis of the blood glucose level 20 min after the glucose injection Women with the highest blood glucose concentration (>8 4 mmol/l) were subjected to the LD subgroup I and the remaining women to the LD subgroup II

The women with gestational diabetes were mostly hospitalized from the beginning of the 36th week of pregnancy They were on a diet with reduced fat and fast carbohydrate content (7 5 MJ = 1 800 kcal/day) routinely prescribed to diabetics and exercised regularly The blood glucose concentration was determined repeatedly None of the women in the LD group developed hyperglycaemia or ketonuria rendering insulin treatment neces

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Abbreviations EIR = early insulin response IVGTT = intravenous glucose tolerance test k value = elimination of glucose LD group = latent gestational diabetes group R group = reference group

Table I *Fasting blood glucose concentration k value fasting serum insulin concentration and E R and LD groups in the third trimester and 2 months post partum (mean ± S D)*

	n	Fasting kB glucose (mmol/l)	k value (per h)	Fasting S insulin (mU/l)	EIR (mU/l)
Pregnant					
R group	9	4 24±0 40	1 06±0 41	14 1±4 7	69 1±36.5
LD group	18	4 82±0 85	0 51±0 10	13 7±7 3	35 1±27.2
p		n s	–	n s	<0 01
Non pregnant					
R group	9	4 43±0 53	0 96±0 30	9 5±3 7	43 4±36 4
LD group	18	4 86±0 35	0 79±0 25	10 2±3 9*	25 8±13 6
p		n s	n s	n s	n s
Individual difference (p)					
R group		n s	n s	<0 05	<0 01
LD group		n s	<0 01	<0 05	n s

n s =not significant
* Data missing for one woman each

sary The foetus was supervised with frequent CTG registrations and determinations of urinary oestriol concentration The intention was to deliver the women at term

Reference group

An IVGTT was performed in the third trimester of pregnancy in 11 women without glucosuria during the current pregnancy a close relative with diabetes or an abnormal obstetrical history in a previous pregnancy Two of these women had a k value of <0 54/h however and were included in the LD group The remaining 9 women aged 22–38 years (median 31) constitute the R group Their body mass just before pregnancy was 47–67 kg (median 57) and relative body mass 77–112% (median 88) The body mass gain during pregnancy was 8–22 kg (median 12) The women were delivered at term

METHODS

A 25 gram IVGTT was performed after an overnight fast during the last trimester of pregnancy as well as two months post partum The carbohydrate content of the diet on the days preceding the test was normal Zero time was set when half of the amount of glucose had been injected i e about 1½ min after the start Capillary blood samples for blood glucose determination were collected before the test and at 10 20 30 40 50 and 60 min Venous blood samples for insulin analysis were taken before the test and at 2 4 6 and 8 min Serum was stored at −20°C until analysis Capillary blood glucose was determined by an o-toluidine method (10) and serum insulin by a commercial double antibody radioimmunoassay (Phadebas insulin test® Pharmacia Sweden) (28) The k value was obtained from the slope of the total blood glucose concentration from a semilogarithmic plot at the interval 20–60 min using the method of least squares The k value was expressed per hour (0 6/h = 1 0%/min) EIR was [illegible] as the mean of the insulin increment above the [illegible] at 2 4 and 6 min The degree of obesity was e[illegible] relative body mass calculated as per cent of [illegible] according to a height weight table (19)

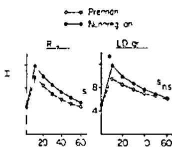
Statistical significance of differences was te[illegible] coxon matched paired signed rank test for pa[illegible] Kruskal Wallis *H* test for unpaired observ[illegible] ference was considered significant for values [illegible] (two-tailed) The Spearman rank correlation [illegible] was used to test linear correlation

RESULTS

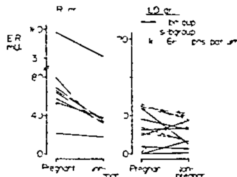
Blood glucose The mean fasting blood glu[illegible] centration was the same in the pregn[illegible] non pregnant state in the LD group and th[illegible] (Table I) The blood glucose concentra[illegible] however lower during the first 40–50 [illegible] IVGTT in the pregnant state than two m[illegible] partum in both groups (Fig 1)

The mean k value was unchanged in the [illegible] (Table I) In four out of ten women in the [illegible] with a k value of <0 54/h during pregn[illegible] mained as low even post partum and in [illegible] woman only a slight increase to 0 62/h w[illegible] These five women belonged to the LD [illegible] i e they had a high blood glucose curve T[illegible] k value post partum in the remaining 11 [illegible] the LD group was 0 90/h

The mean fasting insulin concentr[illegible] [illegible] er during pregnancy than two months po[illegible] in both groups (Table I) No difference [illegible]



Mean blood gluco e curves after an v glucose g p<0 01 ( ) p<0 0 p<0 05 n s not



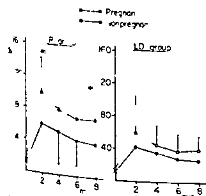
F g 3 Ind dual EIR after an ı v glucose load of 25 g

n the groups e ther during pregnancy or post

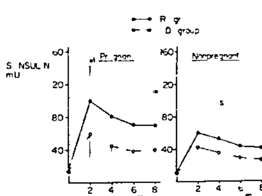
nsu n esponse A substant al decrease of 0 ın EIR was observed post partum ın omen ın the R group compared to the insul n e pregnancy (Table I F gs ? and 3) Ex one lean woman w th a considerable we ght pregnancy (? kg) who had an ex h gh nsul n response the women ın the R showed a moderate ınsul n response ın the gnan sta e w th peak levels at 2 m n of 0-60 mU/l No correlat on was found dur gna cy between the k value and the EIR 13 Po t partum th s correlat on was 0 7? I

hange n EIR from the pregnant to the non s a e n the LD group varied (F g 3) women showed a decrease of the same mag as he women n the R group Others had m u n secret on capacity wh le st ll others had an even h gher EIR ın the non pregnant state Th s ıs illustrated by one woman ın the LD group who had a k value of 0 58/h and an EIR of ? mU/l during pregnancy Two months post partum these values had increased to 1 11/h and 48 mU/l respectively The magn tude of the EIR n the non pregnant state was not decis ve for the ınsul n se cret on capac ty during pregnancy except for wom en w th extremely low responses and subnormal k values

The mean ınsul n concentrat on during pregnancy ın the LD group d d not exceed s gn f cantly the correspond ng value two months post partum unt l at 8 m n ow ıng to a great inter nd v dual variat on n ınsul n secret on capacity (F g ?) The mean ınsul n curve during pregnancy was s gn ficantly lower ın the LD group than ın the R group (Fig 4) Th s d f ference had d sappeared two months post partum Like ın the R group no correlat on was found be tween the k value and EIR ın the pregnant state



Mean S-ın u n curves after an ı v glucose load of stat st cal symbo as ın F g 1



F g 4 Mean S- nsul n curves after an v gluco e load of 25 g Sta t cal symbols as ın F g 1

Table II *EIR in LD group women with high (I) and low (II) blood glucose curve*

	n	EIR (mU/l) Mean	Median	Range	p
Pregnant					
I	9	22 8	21 0	0–48 7	<0 05
II	9	47 5	48 7	2 3–105 0	
Non pregnant					
I	8	18 6	19 9	0 3–34 7	<0 05
II	9	32 1	36 0	13 3–47 7	

n s =not significant

(r=0 04 n s) A significant correlation (r=0 39 p<0 01) was however found two months post partum

As the LD group might be heterogeneous with respect to the degree of impaired glucose tolerance this group was divided according to the height of the blood glucose curve during pregnancy into LD subgroup I with a high and LD subgroup II with a low curve A significantly lower mean EIR was observed in the former subgroup both during pregnancy and two months post partum (Table II) This difference was mainly due to five women who had subnormal k values (<0 66/h) even post partum (Fig 3)

Outcome of pregnancy All women gave birth to living babies including a pair of twins in the LD group One of the twins died in the neonatal period because of congenital heart malformation No further perinatal morbidity was noted The women were delivered at term (≥gestational week 39) except for two in the LD group in whom labour started spontaneously in week 35–36 (birth weights 2 420 and 2 500 g) The Apgar score at 1 and 5 min was normal (9–10) in all babies except one with congenital heart malformation

No significant difference in birth weight was found between children born to women in the LD and in the R group (Table III) Nor was the birth weight increased in children born to women with especially low k values high blood glucose curves or subnormal k values in the non pregnant state

DISCUSSION

The criteria used in this study to screen for gestational diabetes are often considered to indicate a diabetic predisposition (9 20 21 27) Pehrson (21) found however that women fulfilling these c[illegible] had about the same frequency of subnormal [illegible] ues as the women in his reference group W[illegible] with gestational diabetes are thus also foun[illegible] traditional risk groups as has also been ill[illegible] in this study

The blood glucose curve was lower du[illegible] IVGTT in the pregnant state in both normal [illegible] and in women with latent gestational di[illegible] which might be explained by a larger glucos[illegible] partment in pregnancy when the extracell[illegible] ume is increased by about 6–7 litres (11) [illegible] k value in a woman with a low blood glucose [illegible] might reflect counterregulatory mechanism[illegible] than a state of truly impaired glucose tole[illegible] Our LD group might thus be heterogeneous [illegible] respect to true latent gestational diabetes [illegible] further illustrated by the pattern of insulin se[illegible] (discussed below) as well as the non significa[illegible] relation between EIR and the k value d[illegible] nancy The k value should thus not be use[illegible] denominator for latent gestational diabetes [illegible] the blood glucose curve is clearly elevated [illegible] findings in this study emphasize that the [illegible] routine for screening of gestational diabetes [illegible] oral glucose tolerance test as proposed by H[illegible] (9)

The normal glucose stimulated insulin se[illegible] has a biphasic pattern with a fast early and [illegible] and sustained late phase (2 7) Both phases [illegible] as the fasting insulin level are normally e[illegible] in certain conditions for example in obesity [illegible] 15) and during pregnancy (6 17 2?, 25) [illegible] an increased peripheral insulin resistance [illegible] pregnancy this decreased sensitivity is thou[illegible] be induced by several pregnancy hormones [illegible] This is in accordance with the increase[illegible] insulin level as well as the augmented EIR fo[illegible] our R group Patients with manifest diabetes [illegible]

Table III *Birth weights of babies born at [illegible] (gestational week ≥39) (twin pair excl[illegible]*

	n	Birth weight (g) Mean	Median	Range
R group	9	3 668	3 610	3 0[illegible]
LD group	15	3 784	3 800	3 0[illegible]
LD subgroup I	8	3 758	3 780	3 0[illegible]
LD subgroup II	7	3 814	3 900	3 [illegible]

n s =not significant

e as well as of the maturity-onset type are
mz d by a very low or non-detectable early
of glucose stimulated insulin secretion (1
us insulin secretion pattern is also found dur
e pregnancy (6) A decreased and delayed
stimulated EIR has also been considered
enstic for subclinical stages of the diabetic
me in luding the prediabetic state (3) lead
he proposal that EIR measurement might be
screening programmes for diabetes EIR has
ous and unimodal distribution in the popu
I 11 26) Very few individuals in the nor
p lation (1-2%) have as low an EIR as pa
h manifest diabetes and most of these
ls also have subnormal k values indicating
y already have a latent form of diabetes (1)
total risk of developing diabetes during one s
has been calculated to be at least 10-15%
ea (1 8) it is evident that the magnitude of
ll decrease during the evolution of the dia
ndrome from the prediabetic to the manifest
stage Normal EIR has also been found in
members of monozygotic twin pairs one of
had manifest diabetes (4 5 26) and in a
who later developed manifest diabetes (24)
betogenic effect of pregnancy has been used
tudy to obtain further information about the
an e of the level of EIR for the development
tes.

ost evident finding was the inability to in
the insulin secretion capacity during preg
of women who had an impaired glucose tol
in the pregnant state This was most clear
e blood glucose curve was high during the
indica ing a more definitive disturbance in
cose metabolism and in women who even
um had an abnormal glucose tolerance Of
al interest was the finding in some women of
rease in insulin secretion capacity during
indicating a true β-cell insufficiency It
possible to predict the glucose tolerance or
during pregnancy from the magnitude of
response in the non pregnant state ex
women who already then have an abnormal
e tol rance It is thus not the magnitude of the
is important in relation to subclinical forms
s mellitus but the inability to increase or
the insulin secretion to situations in which the
al insulin sensitivity is decreased e g dur
y and perhaps also in obesity
pregnancies terminated successfully except
for one neonatal death from congenital heart malfor
mation in the LD group The mean full term birth
weight was not increased either in the LD group or
in the subgroups with especially low k value high
blood glucose curves or subnormal k values in the
non pregnant state Supervision of pregnancies of
women with latent gestational diabetes—including
a balanced diet of 7 5 MJ exercise control of
blood glucose and urinary oestriol as well as deliv
ery at the optimal time—seems to prevent the devel
opment of manifest diabetes in the mother and en
sures a low perinatal morbidity and mortality and
normal birth weight of the child

REFERENCES

1 Blohme G Intravenous glucose tolerance and early insulin response Studies on a random sample of wom en aged 50 and patients with diabetes mellitus Acta Med Scand (Suppl) 566 1974
2 Cerasi E An analogue computer model for the insu lin response to glucose infusion Acta Endocrinol (Kbh) 55 163 1967
3 Cerasi E & Luft R What is inherited—what is added Hypothesis for the pathogenesis of diabetes mellitus Diabetes 16 615 1967
4 — The occurrence of low insulin response to glucose infusion in children Diabetologia 6 85 1970
5 Daweke H Grote W Gries F A & Lieber meister H Zur Genetik des Diabetes Mellitus Glucosetoleranz Seruminsulin und freie Fettsauren bei eineiigen Zwillingen Dtsch Med Wochenschr 95 983 1970
6 Edstrom K Cerasi E & Luft R Insulin response to glucose infusion during pregnancy A prospective study of high and low insulin responders with normal carbohydrate tolerance Acta Endocrinol (Kbh) 74 87 1974
7 Grodsky G M A threshold distribution hypothesis for packet storage of insulin and its mathemati al modeling J Clin Invest 51 2047 1972
8 Grönberg A Larsson T & Jung J Diabetes in Sweden A clinico-statistical epidemiological and genetic study of hospital patients and death certifi cates Acta Med Scand (Suppl) 477 1967
9 Hadden D R Glucose tolerance tests in pregnancy In Carbohydrate metabolism in pregnancy and the newborn (ed H W Sutherland & J M Stowers) p 19 Churchill Livingstone Edinburgh 1975
10 Hartel A Helger R & Lang H Die Blutzucker bestimmung mit o-Toluidin Methode ohne Eisessig Z Klin Chem 7 14 1969
11 Hedstrand H A study of middle aged men with par ticular reference to risk factors for cardiovascular dis ease Ups J Med Sci (Suppl) 19 1975
12 Hedstrand H Hood B & Ylanen L Insulinsvar och viktfördelning bland medelålders man Lakartid ningen 69 5228 1972
13 Hytten F E & Leitch J Physiology of human

pregnancy Blackwell Scientif c Publ cations Oxford 1966

14 Jackson W P U van M eghem W & Keller P Insul n excess as the init al les on in d abetes Lancet 1 1040 1972

15 Johansen K A new pr nc ple for the comparison of insul n secretory responses II The effect of obes ty on nsul n secret on Acta Endocrinol (Kbh) 74 524 1973

16 — The spectrum of plasma insul n responses in m ddle aged and old non-obese d abet cs with various degrees of metabol c derangement Acta Med Scand 194 157 1973

17 Kalkhoff R K Jacobson M & Lemper D Proges terone pregnancy and the augmented plasma insul n response J Cl n Endocrinol Metab 31 24 1970

18 Kipn s D M Insul n secret on in normal and d abet ic ind v duals Adv Intern Med 16 103 1970

19 Lindberg W Natv g H Rygh A & Svendsen K Høyde og vektundersøkelser hos voksne menn og kv nner Tidsskr Nor Laegeforen 76 361 1956

20 Lunell N O Intravenous glucose tolerance in wom en with prev ously compl cated pregnanc es Acta Obstet Gynecol Scand (Suppl) 4 1966

21 Pehrson S A study of the relat onsh p between some pred abet st gmatas glucose tolerance n late preg nancy and the b rthwe ght of the ch ldren Acta Obstet Gynecol Scand (Suppl) 33 19 4

22 Picard C Ooms H A Balasse E & Conard V Effect of normal pregnancy on glucose a insul n and non esterif ed fa ty acid le el logia 4 16 1968

23 Reaven G M Shen S W Sil ers A & J W Is there a delay n the pla ma insu of pat ents w th chem cal diabetes mell 20 416 1971

24 S mpson R G Benedett A Grodsl Karam J H & Forsham P H Ear insul n release D abetes 17 684 1968

25 Spellacy W N Maternal and fetal metab lat onsh ps In Carbohydra e metabol sm cy and the newborn (ed H W Sutherla Stowers) p 4? Churchill Livings one 1975

26 Sterky G & Thorell J I Early insul n glucose st mulation in s bl ngs of ju er Acta Endocrinol (Kbh) 73 7 1 1973

27 Sutherland H W & Stowers J M chem cal diabetes during pregnancy in travenous glucose tolerance test In C metabol sm in pregnancy and the newbor Sutherland & J M Stowers) p 153 Chu stone Ed nburgh 1975

28 W de L Axén R & Pora h J Radio bent assay for prote ns Chemical cou t bod es to insoluble dextran Immuno 381 1967

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Gangrene Localized to the Lower Limbs in Diabetics

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ICT Over a period of eight years 247 un pat ents with more or less widespread areas us cutaneous erythema on the lower legs 'eet (ncip ent gangrene) or corresponding th cutaneous necrosis (manifest gangrene) mined at our department Of these patients l incip ent and 66% man fest gangrene It d that 75% had open diabetes the others ssified as non-open diabetics In 75% of the ents these lesions accompanied cardiac de ation with or without edema edema of other —in some cases—arterial insufficiency The developed in most patients a short time onset of these precipitating factors Arterial ency alone or together with other precipitat rs was seen considerably less often Edema the main precipitating factor for these le ard ac decompensation as well as edema of due to other causes respond well to treat hen treating such patients with open or non betes it should be taken into consideration grene is a serious condition

f d abetes mell tus gangrene congest ve heart dema

d Scand 08 315 1980

ie of the lower extremities has been re o be 156 t mes more common in d abet cs non-d abet cs in the fifth decade 85 times mmon in the sixth decade and 53 t mes mmon n the seventh (? 9) Gangrene has ed to be the most serious compl cation in large group of d abet cs past middle age (1) usly we described a group of elderly pa th more or less w despread cutaneous areas ma w th or w thout necros s local zed to mbs (11) Most of them had open d a he oral glucose tolerance test curves of the altered n a d abet c direction when com con ols The latter group of patients thus -open d abetes The cutaneous lesions de most often soon after the onset of cardiac decompensat on with or without edema or after edema of other causes In other words these d a betic patients had an altered mode of reaction to the precip tat ng factors mentioned when compared to non-d abetics The skin of the r lower legs also had an altered react on to experimental local traumatizat on with heat and cold compared to non-diabetics (7 11–16) The altered react on was related to the occurrence of m croang opathy and polyneuropathy The presence of diabet c m croan g opathy together w th peripheral polyneuropathy with impaired capacity to vary the blood circulation in the lower l mbs (6 17) was supposed to impede the passage of oxygen from the capillary blood to tissue cells as well as the passage of metabol tes in the opposite d rection The presence of edema further impa rs the passage of these substance Necros s developed often within the areas of cutaneous erythema We have named cutaneous erythema alone incip ent gangrene and cutaneous erythema with necrosis man fest gangrene

Gangrene localized to the lower l mbs of d abetics has been cons dered to be due to atherosclerosis 2 5 10) Many authors however have asserted that th s explanat on is unsatisfactory and have called attent on to the fact that these patients have microang opathy and polyneuropathy (3)

For theoretical as well as pract cal reasons we have cons dered it important to analyse in more detail factors of significance for the development of different types of gangrene in a large number of pat ents In the present nvest gation we have exam ned systematically f there was a close tem poral relat onship between the d fferent precip tat ing factors and the development of gangrene Furthermore the localizat on of the gangrene to the foot alone foot and lower leg or lower leg alone and the factors of importance for the development of gangrene in these local zations were stud ed Par ticular attent on has been pa d to the development of massive gangrene

PATIENTS DEFINITIONS AND METHODS

During 1969–76 we examined 247 unselected patients with gangrene localized to the lower limbs Cutaneous lesions of the lower limbs consisting of areas of obvious erythema the size of a palm of a hand or larger are designated incipient gangrene Necrotic skin lesions with the same localization and with involvement of all layers of the skin are called manifest gangrene In our patients these lesions were almost always surrounded by a zone of erythema Massive gangrene refers to manifest gangrene of most of the forepart of the foot or the whole heel or larger areas The classification into incipient and manifest gangrene is based on the appearance of the lesions when they were first observed Patients with lesions of the medial aspect of the leg were not included in the study because of the common occurrence of varicose lesions in this location Patients with gangrene caused by arterial embolism were also excluded as were patients with erysipelas (8 11 14)

Precipitating factors (Table I) are defined as follows Cardiac decompensation—a diseased state corresponding to class IV of the functional classification of NYHA (4) Edema—swelling so pronounced that finger impression left a clear impression Arterial insufficiency—peripheral coldness and absence of pulses in both the dorsalis pedis artery and the posterior tibial artery Nephrotic syndrome—pronounced proteinuria with hypoproteinemia and edema In patients with deep venous thrombosis the diagnosis was always verified by phlebography

Patients with edema of unknown cause are not a homogenous group Most of them had polyneuropathy and muscular atrophy which ought to impair the venous return due to decreased function of the so called muscle pump (15) This group also includes patients with cardiac decompensation or deep venous thrombosis who did not meet the above diagnostic criteria

The statement that gangrene developed in close temporal relationship to what are called precipitating factors refers to information from the patient himself his family the nurses or the physicians and our own observations Lack of information of a close temporal relationship does not mean that no such relationship existed

The significance of differences between means was calculated using Student s t test Fisher s exact probability test was used to test the difference between groups $P<0.05$ was chosen as the level of statistical significance

RESULTS

Patients with non open diabetes

In the 62 patients without known diabetes oral glucose tolerance tests were performed as described previously (11) The mean blood glucose tolerance test curve area was 15% larger in these patients than in the controls ($p<0.005$)

Different degrees of gangrene in relation to precipitating factors

Patients with incipient gangrene were compared to patients with manifest gangrene (Table I) The mean age was about the same in the two g[roups] namely 68 8 and 67 7 years Twenty two (9%) patients were below 50 years of age Open [diabetes] was more common in patients with man[ifest] than with incipient gangrene (66%) ($p<0.0$…) mean duration of open diabetes was sig[nificantly] longer in patients with manifest than w[ith incipi]ent gangrene (12 1 and 7 9 years respec[tively]) ($p<0.005$)

Precipitating factors for gangrene were re[ported] in 75% of the 247 patients and were more c[ommon] in patients with incipient (84%) than with m[anifest] gangrene (71%) ($p<0.02$) and in pa[tients with] non open (82%) than with open diabe[tes] ($p<0.001$)

Deep venous thrombosis was more com[mon in] patients with incipient (13%) than with m[anifest] gangrene (3%) ($p<0.005$) Arterial insuff[iciency as] the sole precipitating factor was more com[mon in] patients with manifest (9%) than with inc[ipient gan]grene (1%) ($p<0.02$) Arterial insufficiency and combined with cardiac decompensa[tion was] likewise more common in patients with m[anifest] (14%) than with incipient gangrene (5%) …

Edema of all types occurred in 59% of [the] patients and was more common in pa[tients with] incipient (73%) than with manifest gangr[ene] ($p<0.001$) (Table I)

Twenty two patients with massive gangre[ne were] compared with 140 patients with ma[nifest non mas]sive gangrene (Table I) These patients are a[ll] in the group of manifest gangrene P… massive gangrene were somewhat older th[an those] with manifest non massive gangrene and longer mean duration of diabetes but the d[ifferences] were not statistically significant N… significant differences in the frequency of the rate above mentioned precipitating factors insufficiency included Nevertheless all p[recipitat]ing factors together were more common with massive (91%) than with manifest non ma[ssive] gangrene (68%) ($p<0.02$) There were … ences when the simultaneous occurrence precipitating factors was estimated Cardiac compensation with and without edema and simultaneous arterial insufficiency w… mon in patients with massive (18%) than … ifest non massive gangrene (4%) ($p<0$…) cardiac decompensation with edema and … taneous arterial insufficiency (18 and 1…% respectively)) ($p<0.005$) All types of edema …

Du a on pat ents th incipient gangrene man fest g gangrene an l massive g ngrene l cali ed to legs and or feet

	Non open diabetes (n)	Open diabetes: Duration of the disease (y) in age group < 60: <10	≥10	Duration of the disease (y) in age group ≥ 60: <10	≥10	Total: n	%
f gang ene							
es	29	5	6	36	9	85	
n	17	2	3	16	7	45	
	12	3	3	20	2	40	
ge y)	69	55	39	73	74	69	
ra on of d abetes (y)		3	17	4	16	8	
ting factors							
c decompensation							
edema	10	2	1	20 (1)	2	35 (1)	41
out edema	4			3 (1)	1	8 (2)	9
s syndrome w th edema			2			2	2
venous thrombosis w th edema	5	1		3	2	11	13
al insuff c ency only				1		1	1
of unknown cause	4	1	3	3	3	14	17
wn	6	1		6	1	14	17
[g ng ene							
nts	33	11	21	56	41	162	
n	15	6	10	28	22	81	
	18	5	11	28	19	81	
g	73	49	44	73	68	68	
ra on of d abetes (y)		4	23	5	18	12	
ting factors							
c decompensat on							
edema	18 (2)	1		24 (1)	14 (2)	57 (5)	35
out edema	3 (1)	1		9 (1)	6 (2)	19 (4)	12
venous thrombos s w th edema	4			1		5	3
al insuff c ency only	4	1	2	3	4	14	9
of unknown cause		1	11	4	4	20	12
wn	4	7	8	15	13	47	29
gang ene							
ts	5	1	4	6	6	22	
n	1	1	1	4	3	10	
	4		3	2	3	12	
e (y)	76	59	48	78	73	70	
ration of d abetes (y)		3	29	5	19	15	
ting factors							
c decompensation							
edema	3 (1)			3 (1)	3 (2)	9 (4)	41
out edema					2	2	9
venous thrombos s w th edema	1			1		2	9
al in uffic ency only	1	1		1		3	14
nknown cause			3	1		4	18
wn			1		1	2	9

n parentheses ind cate number of pat ents w th concurrent arterial insuffic ency

ore common n patients with massive (68 %) th man fest non massive gangrene (48 %)) (Table I)

f the 247 pat ents reported trauma e g ill fitting shoes as a possible cause of their lesions We were not convinced that the traumatization re ported was of s gn ficant importance for the de velopment of gangrene

Table II Data on 108 patients in whom gangrene developed soon after the onset of prec p . n,] (n,) and on 78 patients in whom only a concomitant precipitating factor was registered (n,)

Precipitating factors	Non-open diabetes: Incipient gangrene n_1	n_2	Manifest gangrene n_1	n_2	Open diabetes: Incipient gangrene n_1	n_2	Manifest gangrene n_1	n_2	Total
Cardiac decompensation									
with edema	9	1	8 (2)	10	14 (1)	11	21 (?)	18	'
without edema	2	2 (3)		3 (1)	1	3 (1)	6 (?)	11 (?)	3'
Nephrotic syndrome with edema					2				100
Deep venous thrombosis with edema	5		4		6		1		100
Arterial insufficiency only			1	3		1	3	6	79
Edema of unknown cause	2	1			9	2	14	6	4
Total	18	4	13	16	32	17	45	41	58
Precipitating factors with edema	16	2	12	10	31	13	36	24	66
Precipitating factors without edema	2	2	2	5	1	4	9	17	33

Figures in parentheses indicate number of patients with concurrent arterial insufficiency

Temporal relationship between precipitating factors and development of gangrene

Precipitating factors were registered in 186 (75%) of the 247 patients In 58% of these 186 patients gangrene developed in close temporal relationship to the precipitating factors (Table II)

As regards patients with non open diabetes and cardiac decompensation with edema but without arterial insufficiency a close temporal relationship was found more often among those with incipient (90%) than with manifest gangrene (38%) ($p<0.02$) As regards patients with non open diabetes and edema of all types together there was also more often a close temporal relationship among those with incipient (89%) than with manifest ga (55%) ($p<0.02$)

A close temporal relationship between the precipitating factors and gangrene was found often in cases with edema (66%) than without (33%) ($p<0.001$) As regards patients with ed close temporal relationship was more o among those with incipient (70%) than wi ifest gangrene (51%) ($p<0.005$)

Localization of the gangrene

The localization of incipient or manifest ga different parts of the lower limbs is shown in III Manifest gangrene localized to the low

Table III Localization of incipient and manifest gangrene to the lower legs and/or feet in 247 p

	Non open diabetes n	%	Open diabetes (n): Age groups < 60: <10 y	≥10 y	Age groups ≥ 60: <10 y	≥10	All ages n	%	T...
Incipient gangrene									
Foot only	10	34	0	1	14	[illegible]	22	39	41
Foot and lower leg	15	52	2	3	20	4	29	5[illegible]	9
Lower leg foot excluded	4	14	3	0	2	0	[illegible]	9	15
Total	29		5	6	36	9	56		
Manifest gangrene									1'
Foot only	17	52	4	20	36	30	90	70	11
Foot and lower leg	1	3	1	0	6	5	12	9	C
Lower leg foot excluded	15	45	6	1	14	6	27	21	'
Total	33		11	21	56	41	1.9		

uluded was more common in pat ents with
xn (45%) than w th open diabetes (71%)
)%. Manifest gangrene local zed to the foot
was more common n patients with open
than w th non-open d abetes ($p<0.05$)
also evident from Table III that the occur
of gangrene localized to the foot alone in pa
w th open diabetes was dependent on the
n of diabetes Pat ents with open d abetes
manifest gangrene on the foot alone had a
mean durat on of d abetes than those w th
s gangrene on the lower leg alone (13 5 and
rs respect ely) ($p<0.01$)

of in erest to note that there were no d ffer
in the occurrence of precip tat ng factors be
the 107 pat ents w th man fest gangrene
ed o the foot alone and the 42 pat ents with
st gangrene localized to the lower leg alone
se temporal relationsh p between the pre
ng factors and the gangrene was observed
that mo e often n the former than the latter
patients The difference was however not
ly s gnificant

SCUSSION AND CONCLUSIONS

patients of th s study were collected with
the occurrence of characterist c lesions of
limbs Most of them had open d abetes
glucose tolerance test curves of the others
gnificantly n a d abet c d rect on when
d w th controls The les ons described are
cal ed diabet c gangrene

nt prec p tat ng factors were demonstrated
5%) of the 247 pat ents w th gangrene In
these 186 pat ents *the lesions developed*
the onset of the prec p tat ng factors
so percentages are undoubtedly under
ts as explained above In the pat ents w th
diabetes and edema *the latter figure was*
90% In most pat ents these factors thus
the lesions

mber of prec p tat ng factors is large The
arterial n uff c ency in our study are of
terest because atheroscleros s has been
to be of outstanding mportance for the
of d abet c gangrene (1 2 5 10) We
arterial insuff c ency as the sole pre
actor n 6% of the pat ents w th non-open
as of those w h open d abetes If pat ents

w th card ac decompensat on w th simultaneous a
ter al insufficiency *are added the figure for pat ent*
w th non open as well as for those w th open d a
betes is about 12% Arterial insuff c ency is thu
not of outstand ng importance for the developmer
of d abet c gangrene It is to be noted that s gns c
arterial insuff c ency were not more common in pa
tients with open than with non-open d abetes Ar
terial insufficiency is however of importance fo
the degree of gangrene Arterial insuff c ency wa
the sole precip tat ng factor in 1% of the patient
with incip ent gangrene in 9% of those w th man
fest gangrene and in 14% of those with man fes
gangrene of so-called mass ve type

The importance of edema for the development o
d abetic gangrene is however striking Edema
alone or together w th other prec p tat ng factors
was registered in no less than 58% of the 247 pa
t ents and was more common n pat ents w th non
open d abetes and in those w th nc p ent gangrene
A close temporal relat onsh p between developmen
of edema and development of gangrene ex sted i
66% of these patients

Both incip ent and man fest gangrene in pat ent
w th open and non open d abetes are to be regarded
as d fferent degrees of intens ty of the same les on
The degree and duration of d abetes and the d ffer
ent prec p tat ng factors are of importance for th
severity and local zation of the les on It is re
markable that s gns of arterial insuff c ency were
found rather seldom and that gangrene most ofte
developed in connect on with edema of d fferen
causes

Our patients are poss bly not representat ve o
patients with d abet c gangrene in general They
have all been hosp tal zed in the Department o
Internal Medic ne probably compris ng a large
number of patients with gangrene and s multaneous
cardiac decompensat on than the surgical depart
ments

Both card ac decompensat on and local edema of
the legs due to other causes respond well to treat
ment Gangrene be ng a serious cond t on th s
should be taken into cons derat on when treat ng
pat ents with open or non-open diabetes The dia
gnos s of non-open d abetes is facil tated by these
patients who often have characterist c s gns and le
s ons local zed to the lo ver l mbs such as poly
neuropathy atroph c sh n spots purpura non
atroph c p gmentat on after prev ous purpura or
redness of the toes (14)

REFERENCES

1 Bell E T A postmortem study of vascular d sease n d abet cs Arch Pathol 53 444 1952
2 — *Atherosclerotic gangrene of the lower extrem t es* in d abet c and nond abet c persons Am J Cl n Pathol 28 27 1957
3 Christensen N J D abet c ang opathy and neuropathy Acta Med Scand (Suppl) 541 1972
4 *The Criteria Comm ttee of the New York Heart As* soc at on D seases of the heart and blood vessels Nomenclature and criteria for d agnosis 6th ed Little Brown & Co Boston 1964
5 Dry T J & H nes E A The role of d abetes in the *development of degenerat ve* vascular d sease w th spec al reference to the incidence of ret n t s and peripheral neur t s Ann Intern Med 14 1893 1941
6 Goadby H K & Downman C B B Peripheral vascular and sweat gland reflexes in d abet c neuropathy *Cl n Sci Mol Med 45 281 1973*
7 Hallmans G Lithner F & Hagg E Early cutaneous react ons to local traumat zat on w th heat in al loxan d abet c rats Ups J Med Sci 83 17 1978
8 Kalbak K The antistreptolys n react on The State *Serum Inst tute Denmark* Copenhagen 1947
9 Lev n M E Med cal evaluat on and treatment In The d abet c foot (ed M E Levin & L W O Neal) pp 1 39 Mosby St Lou s 1973
10 L sa J R Mag day M Gallowa I & ... *Arteriosclerosis w th diabe es mell t ...* patholog cal f nd ngs n 193 d abe ... d abet c pat ents JAMA 1 0 19? 19...
11 L thner F Cutaneous erythema w ... necros s local zed to the legs and fe... *elderly d abet cs* Acta Med Scand 19...
12 — Cutaneous react ons of the extrem ... to local thermal trauma Acta Med Scand ... 1975
13 — Sk n les ons of the legs and feet and ... s ons of the feet in fam l al amyloidosis ... neuropathy Acta Med Scand 199 19? 17...
14 — Purpura p gmentat on and yellow na l ... er extrem t es n d abet cs Acta Med Scand ... 1976
15 — *Lesions of the legs in d abetics and in pat...* fam l al amylo dos s and polyneuropath ... Scand (Suppl) 589 1976
16 Lithner F & H etala S O Skeletal les... feet in d abet cs and the r rela ionship to c... erythema w th or w thout *necrosis on the f...* Med Scand 200 155 1976
17 Moorhouse J A Cartes S A & Do... lar responses in d abet c peripheral ne... Med J 1 883 1966

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Elevated Bone Phosphorus/Hydroxyproline Ratio Following Jejunoileal Bypass Surgery

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ACT The degree of bone mineralization, d as the bone phosphorus/hydroxyproline Hypro) was studied in 33 patients who had ne jejunoileal bypass surgery for massive Low values of bone P/Hypro are expected in lacia We found an elevated mean bone P/ p<0 001) with the highest values in patients e longest postoperative periods (r_s=0 65,) The study indicates that bypass surgery, of vitamin D deficiency, is associated with an d average degree of bone mineralization or a l bone collagen synthesis

rds obesity jejunoileal bypass bone phos ydroxyproline ratio collagen vitamin D defi

d Scand 208 321 1980

eal bypass operation causes small bowel ne with intestinal malabsorption of both vi (5 6 12 23) and divalent cations (3 7 17) s ze in bone composition are complex degrees of osteomalacia with low levels of oxycholecalciferol have been demonstrated histomorphometry in some bypass-oper- tients (6 10 11 17), Some investigators ecreased bone mineral content after bypass (7 12) whereas others have recently re normal values (17)

ges in bone composition can be studied by rphometry of large bone biopsies or by l measurement of the bone phosphorus/ proline ratio (P/Hypro) in minute bone (24) This ratio estimates the degree of neralization which can be taken as an index malacia Low values of bone P/Hypro are t patients with slight vitamin D deficiency

we studied the bone disease following perat on by determining the bone P/Hypro

PATIENTS AND METHODS

Thirty three patients aged 21–59 years (mean 38) with severe and intractable obesity participated in the study An average of 5 6 years (range 2–7) before this study they were treated with an end to-side jejunoileostomy preserving 37 5 cm of the proximal jejunum and 12 5 cm of the terminal ileum The biochemistry of the patients has been published earlier (12 14) All patients have received 1 200 U of vitamin D_3 daily and calcium supplements of 0 5–1 5 g/day since bypass surgery The degree of bone mineralization was measured as bone P/Hypro in iliac crest bone biopsies obtained in local anesthesia (24) Duplicate measurements of the biopsies were used to determine the intraindividual variation in the bone P/Hypro Coefficient of variation was 4 9% (normal 5 0 (24)) The mean values of the duplicate determinations were used in the study Bone P/Hypro values for 137 persons without bone disease served as reference values (25) As the normal bone P/Hypro depends on age the ratio was expressed in per cent of the corresponding normal mean (25)

Spearman s rank correlation test and median test were used for statistical evaluations

RESULTS

Table I shows a tendency towards low levels of serum calcium and serum phophorus Mean serum alkaline phosphatase is elevated The mean bone P/Hypro is significantly higher than normal Only one patient has a subnormal bone P/Hypro (67 1%) Fig 1 demonstrates that the bone P/Hypro increases significantly with increasing length of the period between operation and measurement (r_s=0 65 p<0 001) No significant correlation was found between bone P/Hypro and either the post operative weight reduction (r_s=0 16 n s) or the frequency of stools (r =0 17 n s)

DISCUSSION

The study shows that bone P/Hypro is elevated in patients who have undergone intestinal bypass

Table I *Serum and bone indices in the 33 patients compared to references values*

	Patients		Reference values		
	Mean	S D	Mean	S D	p
Serum					
Calcium(mmol/l)	2 29	0 20	2 47	0 11	<0 02
Alkaline phos phatase (U/l)	49 2	18 2	31 8	7 2	<0 004
Phosphatase (mmol/l)	1 07	0 5	1 15	0 8	<0 08
Bone					
P/Hypro (% of normal)	105 06	9 6	100 0	7 0	<0 01

surgery The increase in P/Hypro with increasing length of time since operation indicates progression of a bone disease The results of serum analysis (Table I) and a tendency towards low values of 25 hydroxyvitamin D 1 25-dihydroxyvitamin D and elevated serum parathyroid hormone reported earlier in some of these patients indicate that they suffer from vitamin D deficiency (12 14)

We determined the bone P/Hypro in order to estimate the average degree of bone mineralization Phosphorus represents the amounts of mineral and *hydroxyproline the amounts of collagen The ratio* has been shown to be an accessible bone index which is low in bone disorders characterized by increased osteoid (2 27 29 30) and it correlates both to indices of importance for bone metabolism (29 30) and to osteoid determined by histomorphometry (28) Our finding of an elevated bone P/Hypro shows that bypass-operated patients do not develop simple osteomalacia and that the bone disease must be more complex Absence of osteomalacia in spite of low values of 25 hydroxy vitamin D agrees with the results reported by Davie et al (8)

P/Hypro is reported to increase with increasing age in normals (25) and in patients with osteoporosis (2) uremia (21 30) and diabetic eye complications (26) Now we have made the same finding in patients after jejunoileal bypass surgery The pathogenesis of this hypermineralization is not clear but a defect in vitamin D metabolism has been proposed in the elderly osteoporotic patient (15) and has been proved in uremia (10) The results of the present study may reflect disturbances in vitamin D metabolism al hough the ba[illegible] not clear

Theoretically an increased bone P H[illegible] due to the combination of a normal deg[illegible] mineralization and elevated phosphoru[illegible] bone mineral or a low hydroxyproline[illegible] collagen An elevated P/Hypro may a[illegible] dicate high amounts of amorphous cal[illegible] phate with an increased P/Ca ratio in b[illegible] (1) Such a condition indicates a high bo[illegible] (1)

A low hydroxyproline content in col[illegible] be due to changes in collagen synthes[illegible] deficiency influences collagen metabol[illegible] 19 20) but changes in the hydroxypro[illegible] collagen have not been reported Defic[illegible] tamin C and iron both of which are kno[illegible] ence proline hydroxylase activity has [illegible] onstrated in bypass-operated patien[illegible] vitro experiments show that the decrea[illegible] hydroxylase activity in vitamin C defi[illegible] causes pro-alpha chains deficient in h[illegible] line As such chains cannot be used for a[illegible] collagen it is assumed from these resul[illegible] lagen deficient of hydroxyproline is u[illegible] Nevertheless such experiments cannot [illegible] possibility that defective collagen [illegible] minor hydroxyproline deficit can be [illegible] Such a defect would explain the high bo[illegible] in our patients The increased urinary e[illegible] hydroxyproline found in gastroin[illegible] sorption (13) may be due to increased bo[illegible] tion but it may also indicate a high e[illegible]

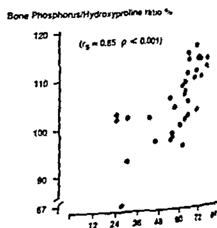


Fig 1 Postoperative bone P/Hypro in the [illegible] studied

…pro-alpha chains which cannot be used …ly of collagen

…lts indicate that patients who have under …oileal bypass operation suffer from a …one disorder due to changes in collagen metabolism

REFERENCES

…A, Pouezat J A & Tochon Danguy H J …tive analysis of amorphous and crystalline …ssue minerals in women with osteoporosis …issue Res 21 457 1976

…ager J C & Birkenhager Frankel D H On …cal significance of the chemical composition … Folia Med Neerl 11 155 1968

…A Greenway F L Barry R E Benfield …iser R L Dahms W Atkinson R L & …s A Surgical treatment of obesity a review …xperience and analysis of published reports …esity 1 331 1977

… Brand J S Neuman W F & Terepka … Some effects of vitamin D_3 on collagen syn… …n rachitic cortical bone Am J Physiol 216 …69

…on J E & Creamer B Plasma levels and …l absorption of 25-hydroxyvitamin D in pa…nth small bowel resection Gut 181 71 1977

…on J E Laker M F Woodhead J S … C Horton L W Ayers A B Bull H J …ton T R E Bone disease after jejunoileal …for obesity Lancet 2 1 1978

… & Christiansen C Calcium absorption and …neral content following intestinal shunt opera… …obesity Scand J Gastroenterol 9 775 1974

…M Lawson D E M & Jung R T Low …25-hydroxyvitamin D without osteomalacia …1 870 1978

…V P & Hern D L Bone matrix studies …Biophys Acta 584 311 1979

…D R & Kodicek E Regulation of 25 hy…drocholecalciferol-1 hydroxylase activity in kidney …thyroid hormone Nature 241 163 1973

…on J D Wise L & Ballinger W F …eal bypass for morbid obesity A critical ap… …Am J Med 64 461 1978

… Lund B Sørensen O H Lund B & …sen M S Impairment of vitamin D and …tabolism in patients with bypass operation for … Acta Med Scand (Suppl) 624 73 1979

…L O Relation to osteoporosis of age and …e-induced changes in the metabolism of col…ld bone Isr J Med Sci 12 620 1976

…3 Hey H Lund B Sørensen O H & …sen M S Vitamin D and jejunoileal bypass …2 764 1978

15 Lund B & Sørensen O H Measurement of 25-hydroxyvitamin D in serum and its relation to sunshine age and vitamin D intake in the Danish population Scand J Clin Lab Invest 39 23 1979

16 Mechanic G L Toverud S U Ramp W K & Gonnermann W A The effect of vitamin D on the stuctural crosslinks and maturation of chick bone collagen Biochim Biophys Acta 393 419 1975

17 Parfitt A M Miller M J Frame B Villanueva A R Rao D S Oliver I & Thomson D Metabolic bone disease after intestinal bypass for treatment of obesity Ann Intern Med 89 193 1978

18 Prockop D J Kivirikko K I Tuderman L & Guzmann N A The biosynthesis of collagen and its disorders N Engl J Med 301 13 1979

19 Raisz L G Maina D M Gworek S C Dietrich J W & Canalis E M Hormone control of bone collagen synthesis in vitro Inhibitory effect of 1 hydroxylated vitamin D metabolites Endocrinology 102 731 1978

20 Russell J E & Avioli L V 25 Hydroxycholecalciferol-enhanced bone maturation in the parathyroprivic state J Clin Invest 56 792 1975

21 Schaadt O & Tougaard L The degree of bone mineralization in chronic renal failure estimated from phosphorus/hydroxyproline ratio in bone biopsies Acta Med Scand198 91 1975

22 Scott H W Jr Dean R & Shull H J New considerations in use of jejunoileal bypass in patients with morbid obesity Ann Surg 177 432 1973

23 Teitelbaum S L Halvorson J D Bates M Wise L & Haddad J C Abnormalities of circulation 25 OH vitamin D after jejunal ileal bypass for obesity Ann Intern Med 86 289 1977

24 Tougaard L The degree of bone mineralization in bone tissue The phosphorus/hydroxyproline ratio determined on small amounts of bone tissue Scand J Clin Lab Invest 32 351 1973

25 — The degree of mineralization in normal bone tissue estimated as the phosphorus to hydroxyproline ratio Scand J Clin Lab Invest 35 285 1975

26 Tougaard L Ditzel J & Rødbro P Bone mineral content and degree of mineralization in diabetes mellitus Acta Edocrinol 88 72 1978

27 Tougaard L Hau C Rødbro P & Ditzel J Bone mineralization and bone mineral content in primary hyperparathyroidism Acta Endocrinol 84 314 1977

28 Tougaard L Melsen F & Mosekilde L Bone phosphorus/hydroxyproline ratio and bone histomorphometry in normals Scand J Clin Lab Invest 38 89 1978

29 Tougaard L Rickers H Rødbro P Hess Thaysen E Christensen M S Lund B & Sørensen O H Bone composition and vitamin D after Pólya gastrectomy Acta Med Scand 202 47 1977

30 Tougaard L Sørensen E Christensen M S Brøchner Mortensen J Rødbro P & Sørensen A W S Bone composition and parathyroid function in chronic renal failure Acta Med Scand 202 33 1977

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Membranous Glomerulopathy in a Patient on Captopril

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ACT This case report describes a patient ssential hypertension in whom captopril dur en months resulted in a nephrotic syndrome al biopsy specimen revealed membranous ulopathy stage I After withdrawal of the urinary protein loss disappeared within ten However a second biopsy three months later owed granular depos tion of IgA IgG IgM in the glomerular basement membrane and ged subep thelial electron dense deposits on n microscopy Glomerular filtration rate re- normal during the observation period

ords captopril convert ng enzyme inh bit on ous glomerulopathy nephrotic syndrome

Med Scand ?08 325 1980

?n enzyme inh b tion by captopril (1 (D ano-?-methyl 1-oxypropyl)-L prol ne) ap- to be very effect ve in the treatment of on (3 15) in some of the patients er only after comb nat on with sodium de (3 15) Reduct on in blood pressure (BP) captopril therapy results to a great extent blockade of angiotens n II format on (1 15) er the drug also inhib ts extrapulmonary gen n of angiotens n II (13) remains to be eluci The same holds for the contribution of capto- duced dim n shed bradykin n hydrolysis to crease n BP (11 1? 18)
Untoward effects of captopril include fever (3 7 sh (3 15) angioneurotic oedema (15) a (19 aphthous ulcers of the mouth (17) and ukocytos s (?) Most of these s de-effects are e (3 7 15 19) Nephrotic syndrome and um sickness-l ke syndrome have also been ted occasionally in pat ents on captopril (10

This case report describes in detail the first pa tient with essential hypertension in whom nephrotic syndrome developed while on captopril Secondly an account of the effects of withdrawal of captopril treatment on urinary protein loss and morphological changes in the kidney of this patient will be given

CASE REPORT

The patient was a 48-year-old woman in whom hyperten s on (155/100 mmHg) was found in 1965 Her med cal h story included an appendectomy and a hysterectomy Two pregnancies had been uneventful Her mother had also suffered from hypertens on

In 1977 the pat ent was referred to our Outpat ent Cl n c because her BP was ?60/140 mmHg sup ne and ?70/150 mmHg upright desp te treatment w th sod um restrict on chlorthalidone and α methyldopa Chest X ray and ECG showed no abnormal t es Fundoscopy revealed hyperten s ve changes of K W grade II Rap d sequen e i v uro- graphy renography and renal angiography were normal Without therapy serum sod um was 139 mmol/l serum potassium 4 3 mmol/l and serum creatinine 77 μmol/l Vanillylmandelic ac d excretion was normal The urine contained ne ther prote n nor glucose and the urinary sed ment was normal A diagnosis of essential hyperten s on was made and she was treated with sod um restric t on hydrochlorothiazide potass um suppletion and clonid ne

In Oct 1978 the ant hypertensive therapy was d scon tinued because her BP control was unsatisfactory (?00/1?0 mmHg sup ne) The BP rose to ??0/140 mmHg At that t me serum sod um was 139 mmol/l serum potass um 4 ?

Repr nt req ests to S J Hoorntje M D Department of Med c ne State Un vers ty Hosp tal Oosters ngel 59 9713 EZ Gron ngen The Netherlands

Abbrev at ons ANA ant nuclear antibod es ERPF effective renal plasma flow FF filtration fract on GBM = glomerular basement membrane GFR glomerular filtration rate PAC plasma aldosterone concentration PRA = plasma ren n activ ty MGP membranous glomerulopathy BP blood pressure







Fig 1 (*a*) Light microscopy [illegible], (*b*) electron microscopy [illegible] and (*c*) immunofluorescence microscopy (×1[illegible]) of the renal biopsy in May 1979

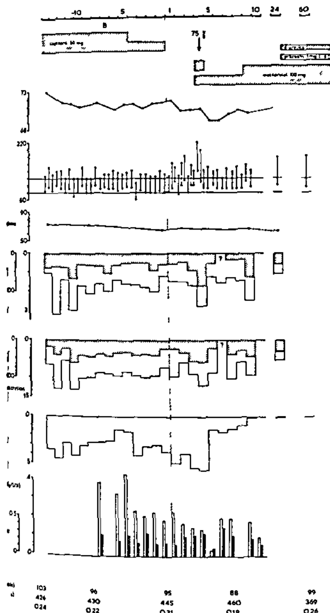


Fig 2 Effect of withdrawal of captopril on BP urinary protein loss PRA (□) PAC (▨) and renal function 75 γc = 75 gamma clonidine *H* = 50 mg hydrochlorothiazide

and serum creatinine 71 μmol/l Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were and 380 ml/min respectively filtration fraction was 0 25 (4) The urine contained no protein and the sediment was normal again Antinuclear antibodies (ANA) were not found Supine plasma renin activity (PRA) amounted to 0 8 nmol A_I/l/h and plasma aldosterone concentration (PAC) to 0 47 nmol/l (12 14) An acceptable BP control (130/80 mmHg) was obtained with 50 mg captopril t i d and the patient remained normotensive during the monthly visits to the Outpatient Clinic GFR and ERPF to 426 ml/min

In February and March 1979 slightly positive (titers 1 10) (homogeneous pattern) were disclosed Antibodies against native DNA were absent In April 1979 the patient noticed oedema of the feet Proteinuria was present (5 g/24 h) On admission in May 1979 her BP was normal (120/80 mmHg) as was the urinary sediment Hypoalbuminaemia (2 6 g/100 ml) and hypercholesterolaemia (10 4 mmol/l) existed Serum creatinine was 74 μmol/l GFR 96 ml/min ERPF 430 ml/min and FF 0 22 ANA were positive (titer 1 10) but antibodies against native DNA negative Complement (C_{3c}) amounted to 124% of standard serum There was no cryoglobulinaemia A renal biopsy was performed and no proliferative or exudative changes were found on light microscopy (Fig 1*a*) Electron-dense deposits along the subepithelial side of the glomerular basement membrane (GBM) were revealed on electron micro

scopy (Fig 1*b*) Immunofluorescent studies showed IgA IgG IgM and C_3 distributed in a granular pattern in the GBM (Fig 1*c*)

Captopril was discontinued and BP rose thereafter to preexisting values (Fig 2) PRA decreased and PAC increased Hypertension was now treated with hydrochlorothiazide triamterene metoprolol and prazosin A satisfying BP control was achieved Interestingly proteinuria disappeared completely within 10 days after withdrawal of captopril (Fig 2) A second biopsy at the end of Aug 1979 showed unchanged immunofluorescence and unchanged subepithelial electron-dense deposits Light microscopy was normal again At that time there was no proteinuria Urinary sediment was normal ANA had disappeared GFR amounted to 99 ml/min ERPF to 369 ml/min and FF to 0 26

DISCUSSION

The renal biopsy findings in our patient are consistent with the diagnosis of membranous glomerulopathy (MGP) stage I (5) We have made similar findings in another patient who developed a captopril induced serum sickness like syndrome (10) Proteinuria during captopril treatment has also been noticed by other investigators who found an early stage of MGP in the renal biopsy specimens as well (dr J Knill personal communication) Thus the occurrence of MGP in patients on captopril is unlikely to be fortuitous and patients taking this drug should be carefully monitored However the frequency of proteinuria during captopril treatment is hardly 1 % and can be transient despite continuing administration of the drug (Squibb & Sons Inc) Moreover renal function (i e GFR) seems not to be compromised (9) The way in which captopril induces MGP in some patients is unknown The similarity of this immune complex glomerulopathy to MGP induced by d penicillamine is however striking

It was further remarkable that the proteinuria in our patient disappeared completely within 10 days after withholding the drug In other drug induced immune complex glomerulopathies for instance d penicillamine induced proteinuria disappears after a much longer time lag and more in accordance with the disappearance of the morphological changes Therefore we wonder if captopril by decreasing the generation of angiotension II and by inhibiting the degradation of bradykinin might facilitate glomerular protein loss when immune complex deposition has taken place In this respect it is noteworthy that the protease inhibitor trasylol reduces aminonucleoside induced proteinuria in the rat (8) [illegible] inhibits generation of kallikrein and the[illegible] generation of bradykinin It is even possib[illegible] pharmacological action of captopril [illegible] played a permissive role in the deposition or formation of immune complexes The [illegible] these immune complexes remains howe[illegible] elucidated

REFERENCES

1 Atlas S A Case D B Sealey J E Lara[illegible] & McKinstry D N Interruption of the [illegible]giotensin system in hypertensive patients b[illegible] induces sustained reduction in aldoster[illegible] potassium retention and natriuresis H[illegible] 1 274 1979
2 van Brummelen P et al & Amann F [illegible] Captopril associated agranulocytosis Lan[illegible] 1980
3 Case D B Atlas S A Laragh J H & Se[illegible] E Clinical experience with blockade of the [illegible]giotensin–aldosterone system by an oral c[illegible] enzyme inhibitor (SQ 14 225 captopril) in hy[illegible]sive patients Progr Cardiovasc Dis [illegible]
4 Donker A J M van der Hem G K S[illegible] & Beekhuis H A radioisotope method f[illegible]taneous determination of the glomerular filtr[illegible] and the effective renal plasma flow N[illegible] 20 97 1977
5 Ehrenreich T & Churg J Pathology of m[illegible]nous glomerulopathy Pathol Annu 3 14[illegible]
6 Freedlander A E Fyhrquist F & H[illegible] G In Methods of hormone radioimmunoassa[illegible] B M Jaffe & H R Behrman) p 4[illegible] Press New York and London 19[illegible]
7 Gavras H Brunner H R Turini G A [illegible] G R Tift C P Cuttelod S Gavras I [illegible]vich R A & McKinstry D N An[illegible] effect of the oral angiotensin converting en[illegible]hibitor SQ 14225 in man N Engl J Med [illegible] 1978
8 Gilboa N Smith J A Largent J & L[illegible] Protease inhibitor trasylol (Tr) reduces the a[illegible]leoside (AN)-induced proteinuria in the ra[illegible] p 12A The American Society of Neph[illegible] 1979
9 Hoorntje S J Kallenberg C G M [illegible] Donker A J M The T H & H[illegible] Immune complex glomerulopathy in pa[illegible] with captopril Lancet 1 121[illegible] 19[illegible]
10 Hoorntje S J Weening J J Kallenberg C [illegible] Prins E J L & Donker A J M Se[illegible] like syndrome with membranous gl[illegible] patient on captopril Lancet 2 1[illegible] 19[illegible]
11 Hulthén L & Hökfelt B The effect of t[illegible] ing enzyme inhibitor SQ 20 881 on [illegible] giotensin–aldosterone and catecholamines a[illegible] to blood pressure in hypertensive patients [illegible] Scand 204 497 1978

-aston C I Millar J A McGrath B P & ...thews P G Long term effects of captopril (SQ 225) on blood pressure and hormone levels in ...ntial hypertension Lancet 2 493 1979

...rd D Koerner T & O Donohue J K ...hanism of angiotensin I converting enzyme in ...ation by SQ 20 881 (<Glu Trp-Pro Arg Pro Gln Pro-Pro) in vivo Further evidence for extrapulmo ...y conversion Hypertension 1 13 1979

...e J J Boonman R Woldring M G & Donker J M Special problems in the radioimmunoassay ...plasma aldosterone without prior extraction and ...fication Clin Chim Acta 84 329 1978

...s E J L Converting-enzyme inhibition Experiences with captopril in hypertensive patients Thesis van Gorkum Assen 1979

16 Prins E J L Hoorntje S J Weening J J & Donker A J M Nephrotic syndrome in a patient on captopril Lancet 2 306 1979

17 Seedat Y K Aphthous ulcers of mouth from captopril Lancet 2 1297 1979

18 Swartz S L Williams G H Hollenberg N K Moore T J & Dluhy R G Converting enzyme inhibition in essential hypertension the hypotensive response does not reflect only reduced angiotensin II formation Hypertension 1 106 1979

19 Vlasses P H & Ferguson R K Temporary ageusia related to captopril Lancet 2 526 1979

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Pseudotumor Cerebri in Pseudohypoparathyroidism

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ACT A case of hypocalcemia with elevated TH but normal renal response of cAMP and te to PTH infusion is reported The patient papilledema since many years probably due sting hypocalcemia

ds pseudotumor cerebri pseudohypoparathy

Scand 208 331 1980

ypoparathyroidism (PHP) is the first dis which a d fective response to a hormone in wise normal organ has been recognized (1) uld be demonstrated by an inadequate phos response to exogenous parathormone The patients generally have typical dys signs oligophrenia and laboratory signs parathyroidism resistant to PTH Cyclic te monophosphate (cAMP) in urine has also own to be resistant to PTH This has been a test for PHP A few PHP patients with a rmal response of cAMP to PTH but with a e phosphaturic response have however ported This type of PHP has been called (3)

tient with hypocalcemia and elevated PTH mal renal response (phosphate and cAMP) enous PTH has recently been reported (5) tient had reduced levels of 1 25 dihydroxy lciferol Therapy with 1 25-dihydroxychole ol restored the calcemic response to PTH to This could be explained by skeletal but not esistance usually present in ordinary PHP

CASE REPORT

born in 1923 had tetanic symptoms probably since year and during childhood and adolescence He pitalized in 1936 with the diagnosis of tetany calcium was at that time 6 3 mg/100 ml He re vitamin D for a short time and has since then d no tetany or other neurologic symptoms

In 1952 the patient was admitted because of headache He had no neurologic symptoms or signs A papilledema with a protrusion of 3–4 diopters was found Because of this papilledema he was then on several occasions investi gated with carotid angiographies as well as encephalography and ventriculography No cerebral tumor could be found but the papilledema persisted Serum calcium was not checked at that time In recent years the patient has been unable to work because of lumbar pains and obesity

Hypocalcemia was noted once again in Feb 1976 The sole symptoms possibly related to this hypocalcemia were paresthesias in the ulnar fingers of both hands Physical examination revealed an obese man with a weight of 121 kg and height of 178 cm Normal hands no Chvostek s signs slight hypertension no cataracts X-ray of the skull revealed no calcifications of the basal ganglia X rays of the lumbar columna and hands were normal apart from spondylarthrosis Except for hypocal emia 1 8–2 0 mmol/l the routine laboratory investigations showed nor mal findings Serum phosphate serum magnesium and hematology were normal Treatment with calcium gluconate 2 g/day and dihydrotachysterol 0 4 g twice daily was initiated The therapy continued for six months but was withheld one week before the first investigation The same treatment was reinstituted and continued for another two months and was withheld another ten weeks before the second investigation

METHODS

Food was withheld for 12 hours but water intake ad lib was permitted before the study On the day of the study a Foley catheter was inserted in the bladder The patient drunk 250 ml water hourly from 6 00 a m until noon Urine was collected at 30-min intervals from 8 00 a m till noon PTH 300 USP in 50 ml of 0 9 % sodium chloride and 0.5 % human serum albumin were infused at 9 00 a m The same procedure was carried out in a volunteer without signs of renal or parathyroid disease Blood samples for calcium and phosphorus before and after PTH administra tion were unfortunately drawn only in the last study Urine portions were immediately analyzed for calcium and inorganic phosphorus PTH was estimated according to Almqvist et al (2) The method of Steiner et al (6) was used for determination of cAMP

Abbreviations PHP=pseudohypoparathyroidism PTH parathormone cAMP=cyclic adenosine monophos phate



Fig 1 Liver biopsy ... month of carbam... treatment showing ... caseous granulom... changes with lym... epithelioid cells ... nuclei ed ... toxylin-eosin ...

vacuolization but no granulomas Mitochondrial antibody examination (not performed during the first admission) was positive 1/100 Five months later this test was negative Antibodies against nuclei and smooth muscle were negative Bacteriological and serological tests for tuberculosis toxoplasmosis mononucleosis viral hepatitis cytomegalovirus mycoplasma parainfluenza influenza adenovirus ornithosis were negative

DISCUSSION

This case report concerns a patient with reversible granulomatous hepatic reaction There are good reasons to associate the disease with coincidental carbamazepine treatment The illness started 3 weeks after initiation of the drug No ... was given during this time The Liver ... disappeared in less than one week af... of the drug During a 4-day provocation carbamazepine was reinstituted and the symptoms with pain fever and elevated ... ALAT reappeared Reversible elevation ... enzymes is a known side-effect of this drug ... other explanation of this reversible granul... hepatic disease could be found neither ... logically nor serologically

Table I *Sequential changes in pertinent biochemical findings*

	Normal values	Jan 15	Jan 25	Feb 2[b]	Feb 22
ESR (1 mm/1 h)	2–15	22		39	7
Leukocytes (×10⁹/l)	4–9	13 1	9 4	9 5	6 0
Eosinophils (×10⁶/l)	40–440	650		523	120
Total bilirubin (μmol/l)	4–21	17 1	3 8	5 3	9 0
ALP (μkat/l)	0 8–4 8	8 9	5 0	1 7	1 6
ASAT (μkat/l)	<0 6	5 0	0 4	0 7	0 3
ALAT (μkat/l)	<0 6	4 5	0 7	0 8	0 3
LDH (μkat/l)	3 8–6 7	11 1			6 1

[a] Carbamazepine given Dec 18 1978–Jan 16 1979 (30 days) [b] Carbamazepine given Jan 29 1979–Feb 1 1979 (4 days)

One question to be answered is Can gra... be formed during a 4 week period? The granulomas induced by phenylbutazone ... oxyphenylbutazone have shown a brief ... tion period (up to 24 days) and lack of co... with dosage (1 8–70 0 g) (3) In an experim... tem I have observed the formation of m... leated giant cells in 13 days (4) In ... seems quite possible that one mont... bamazepine treatment may result in th...

The reversible appearance of ... antibodies is interesting from an ... point of view Do these antibodies play a ... pathogenetic role in this disease or are they ... as a result of a toxic unspecific hepat... is not possible to comment on this ... report

The prognosis in this type of drug-induced ... tion seems to be favorable if ... drug is discontinued in due time The ...

se showed complete disappearance of the ranulomas and reports of serious liver reac f this type are rare This report and others (5 hasize the necessity of tests for hepatic dys n in patients receiving carbamazepine

REFERENCES

1 1980 (Pharmaceutical specialties in Sweden) medelsinformation Stockholm 1980
2 an J C & Perry J E Granulomatous tis An analysis of 63 cases and review of the ture Ann Intern Med 65 1081 1966
3 Ishak K G Kirchner J P & Dhar J K Granulomas and cholestatic hepatocellular injury associated with phenylbutazone Dig Dis 22 611 1977
4 Levander H G Formation of multinucleated giant cells from circulating blood cells cultivated in diffusion chambers Folia Haematol (Leipzig) 103 631 1976
5 Ramsay I D Carbamazepine-induced jaundice Br Med J 4 155 1967
6 Sherlock S Diseases of the liver and biliary system 5th ed Blackwell Scientific Publications Oxford 1975
7 Simmons F Feldman B & Gerety D Granulomatous hepatitis in a patient receiving allopurinol Gastroenterology 62 101 1972
8 Zucker P Daum F & Cohen M I Fatal carbamazepine hepatitis J Pediatr 91 667 1977

ANNOUNCEMENTS

The French Association of Haemophiliacs International Prize of F F 15 000 will be awarded for the fourth time in 1981 The regulations in French or English will be forwarded on request by the Selection Commitee Association Française des Hémophiles C N T S 6 rue Alexandre Cabanel 75739–Paris Cedex 15 France The work submitted for the Prize must reach the Secretariat of the Selection Committee by March 15 1981 at the latest

The British Journal of Pain will commence publication early in 1981

As pain is a ubiquitous and important symptom in many diseases it is hoped that this new Journal will arouse interest in a wide range of medical disciplines The intention is to provide a forum for original work a articles related to the cause and treatment of The primary aim of the new Journal is to pub of a practical clinical nature although bas (animal or laboratory) and philosophical pape be refused

The Journal will have an independent Board ment not directly connected with any Socie at first appear quarterly

The Editorial Committee will be pleased papers for publication Instructions for auth scription forms are available from the Editor o lisher British Journal of Pain John Sherratt & 78 Park Road Altrincham WA14 5QQ England

Acta Med Scand 208 337–340 1980

CONTINUED DEBATE

Dietary Fatty Acids and Ischaemic Heart Disease

D V Hamilton E J A Lea and S P Jones

From Addenbrooke s Hospital Cambridge and Membrane Laboratory School of Biological Sciences University of East Anglia Norwich Norfolk England

...mportance of prostacyclins in the prevention ...mbosis has led to interest in the role which fatty acids which are precursors of prostacyc ...ght play in the prevention of ischaemic heart ...e Increase in certain fatty acids in the diet ...advantageously influence platelet function

...tance of prostacyclins

...et aggregation represents an early event in the ...ex chain of events which leads to the forma...f a thrombus Two groups of clinical com...s which affect platelet aggregation are the ...cyclins (PGI) and thromboxanes (TxA) Pros...lins are formed by the endothelial linings of ...y blood vessels and are the most potent in...rs of platelet aggregation yet discovered In ...ion prostacyclins are vasodilators Throm...es on the other hand are produced by ...ets and promote their aggregation and are also ...onstrictors A balance between the forma...nd activities of these two substances pros...lins and thromboxanes is important for the ...ostasis of the cardiovascular system (11) An ...ance in the favour of thromboxanes will result ...increased tendency to thrombosis and an ...n e in the favour of prostacyclins a tendency ...dme It is of relevance that prostacyclin pro...n has been shown to be reduced in human ...sclerot c plaques (1)

... s of prostacyclins

...hromboxanes and prostacyclins are produced ...the same polyunsaturated fatty acids but by ...ent enzymes There are three different types ...h compound the 1 2 and 3 series each aris...rom a different polyunsaturated fatty acid ...idonic acid (C20 4w6) and eicosapentaenoic (C20 5w3) are precursors of two different ...l of prostacyclins and thromboxanes (Fig 1)

The former arachidonic acid originating from the w6 fatty acids gives rise to a prostacyclin (PGI) and a thromboxane (TxA_2) The latter eicosapen taenoic acid originating from the w3 fatty acids produces a prostacyclin (PGI_3) and a corresponding thromboxane (TxA_3) Both prostacyclins (PGI_2 and PGI_3) are antiplatelet aggregating agents However TxA_3 derived from eicosapentaenoic acid is less active as a promoter of platelet aggregation than TxA_2 If therefore the pathway which predominates in any individual preferred the formation of PGI_3 and TxA_3 the haemostatic balance might be shifted away from the thrombotic side of the system thus affording some protection against thrombosis

The essential difference between the two series PGI_2 TxA_2 and PGI_3 TxA_3 resides in the nature of the third bond counting from the terminal methyl group of the fatty acid molecule in the w3 series this bond is double whereas it is single in the w6 series The conversion of fatty acids of the w6 series into fatty acids of the w3 series does not occur in man

Clinical studies of the role of prostacyclin precursors

Although diets containing different fatty acids may affect cholesterol levels and atherosclerosis in the same way they may have different effects on thrombogenesis Epidemiological studies of the in cidence of ischaemic heart disease have led to some appreciation of the importance of diet in the aetiology of ischaemic heart disease

Deaths from cardiovascular disease are rare among Eskimos and this has been attributed to an increased bleeding tendency which they possess Eskimos consume large quantities of w3 polyun saturated fatty acids precursors of PGI_3 and platelet lipid analysis has demonstrated an in creased proportion of these polyunsaturated fatty

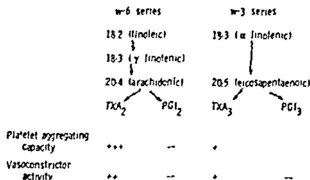


Fig 1 Metabolism of some polyunsaturated fatty acids Number of positive or negative signs indicate the potency of the compound in promoting or inhibiting the particular physiological action

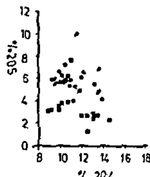


Fig 2 Fatty acids of the lipids of human er Plot of % C20 5 versus C20 4 ■ = Pa from myocardial infarction ● = controls Th apparent relationship between % C20 4 and bet The percentage C20 5 in heart patients is 3 9 in controls 6 06±0 29 (mean ± S E M) In the graphic analysis the peak containing C20 5 Subsequent studies have separated these two shown that the latter is small

acids in the platelets (3) In particular platelet eicosapentaenoic acid levels in Eskimos are markedly elevated when compared to the levels found in Danes in whom ischaemic heart disease is relatively common (Table I) Thus the low incidence of myocardial infarction in Eskimos may result from the increased synthesis of PGI_3 from eicosapentaenoic acid resulting in an alteration of the balance between aggregation and inhibition of aggregation of platelets towards the latter

Alteration in the diet to achieve a similar fatty acid pattern as Eskimos may therefore prevent the development of coronary thrombosis A study of the administration of eicosapentaenoic acid to volunteers in their diet in the form of 650 g mackerel per day has shown that after only one week on this diet considerable changes in the fatty acid concentration in the plasma and platelets occurred (16) A marked decrease in arachidonic acid an crease in eicosapentaenoic acid resulted associated reduction in platelet aggrega TxA_2 synthesis (Table I)

Further support for the importance of ei taenoic acid in thrombosis has come from study using the erythrocyte membrane as probe to compare the fatty acid compo group of 20 patients aged below 65 ye myocardial infarction and a group of matched healthy controls (8) There wa nificant difference between the level of ara acid in the patients and controls but th however a highly significant difference of eicosapentaenoic acid Markedly depre ues were found in those patients who had myocardial infarction (Table I and Fig 2)

What of the relationship between previ studies and newer theories of the role of p lins and thromboxanes in the aetiology nary thrombosis? Low density lipopro correlate positively with ischaemic (6) have been found to inhibit in vitro p clin formation by human endothelial Moreover high density lipoprotein which negatively with ischaemic heart disease increased by fish which is rich in w3 precursors of PGI_3 (10) The failure show benefit from diets rich in polyunsat ty acids may be due to an incorrect polyunsaturated fatty acids

Table I *Percentage concentration of eicosapentaenoic acid*

Group	C20 5w3 (%)	Source
Platelets		
Eskimos	8	Dyerberg & Bang (3)
Danes	0 5	
Controls	1	Siess et al (16)
After mackerel diet for 6/7	5 1	
Erythrocytes		
Controls	6	Lea et al (8)
Patients with ischaemic heart disease	3 9	

II *Ratio of w6 w3 fatty acids and percent eicosapentaenoic acid in various foods*

	Ratio w6 w3	C20 5w3 (%)
	0 22	17 8
	0 29	14 3
	0 13	6 0
	0 42	7 1
n	0 13	13 5
	0 36	9 6
	0 06	15 8
	0 28	11 9
	0 38	14 0
	0 34	13 2
	0 34	10 8
	2 3	Trace
	19 0	Trace
	1 0	Trace
	8 2	Trace
	0 9	–
	100	–
	72	–
	12	–
(zero erucic)	2 0	–
	147	–
r (Northern)	220	–
	7 5	–

ietary recommendations

the past forty years the incidence of isch eart disease has considerably increased he same period the British diet has changed rably In particular the w6 w3 ratio of the gradually increased mainly because of the ng consumption of linoleic acid rich plant e form of margarine and cooking oils but to extent due to a decreased consumption of has been calculated that over the last forty e w6 w3 ratio has increased from 6 1 to 9) A return to the diet of yesteryear might ficial in the prevention of thrombosis This e achieved in two ways Firstly an increase let of fatty acids of the w3 series together decrease in the fatty acids of the w6 series esult in an increased synthesis of PGI_3 and a e of TxA_2 Table II shows those foods which a low ratio of w6 w3 fatty acids in particu which might be beneficial to achieve this e However controversy still surrounds the question as to whether elongation and desaturation of α linolenic acid (C18 3w3) does indeed occur in man (4 15) If it does occur then enrichment of the diet with α linolenic acid (e g olive oil soybean oil) would provide the necessary fatty acid for PGI_3 synthesis

The other alternative is to increase in the diet those foods rich in eicosapentaenoic acid which as can be seen from Table II are mainly fish Although it has been claimed that diets rich in poly unsaturated fats may be associated with cholelithi asis there is no evidence that they are carcino genic (5)

Prostacyclins in other diseases

Increased prostacyclin synthesis by dietary modifi cation may be beneficial not only in the prevention of coronary thrombosis but also in other medical conditions Prostacyclin production by blood ves sels from patients with diabetes is depressed (7 17 18) It has been suggested that vascular complica tions in such patients may be due to deficient pros tacyclin production and enhanced platelet aggrega tion and adhesiveness Low concentrations of 6-Oxo-PGF1a a metabolite of prostacyclin have been found in diabetics (2)

In the haemolytic uraemic syndrome charac terised by widespread microthrombosis predomi nantly in the kidneys a deficiency of prostacyclin production by the vascular endothelium has been found (14 20)

Of recent interest has been the role of prostacyc lin in pregnancy and the possibility that a relative deficiency of prostacyclin might be a factor in the pathogenesis of pre eclampsia (9) A reduction of foetal vascular prostacyclin activity has been shown in those pregnancies complicated by pre eclampsia (13)

Conclusion

Before a change in diet is recommended for patients with ischaemic heart disease or for populations at risk of developing ischaemic heart disease more evidence is required There are however some indications that diets rich in eicosapentaenoic acid may be beneficial by virtue to the role of this fatty acid in the synthesis of PGI_3 Dietary control of the function of the platelet and pr in production by the vascular endothelium ing poten- tial in the prevention addition

there mas be other diseases in which endogenous production of prostacyclin might be beneficially increased

REFERENCES

1 D Angelo V Villa S Myslrwiec M Donati, M B & de Gaetano G Thromb Haemostas 39 535-536 1978
2 Dollery C T Friedman L A Hensby C N Kohner E Lewis P J Porta, M & Webster, J Lancet 2 1365 1979
3 Dyerberg J & Bang, H O Lancet 2 433-435 1979
4 Dyerberg J Bang H O & Agaard O Lancet 1 199 1980
5 Ederer F Leren, P Turpeinen P & Frantz, I D Lancet 2 203-206 1971
6 Gordon T Castelli W P Hjortland M C Kannel W B & Dawber T R Am J Med 62 707-714 1977
7 Johnson M Harrison H E Raftery A T & Elder J B Lancet 1 325-326 1979
8 Lea, E J A. Jones S & Hamilton D V Excerpta Med Int Congr Ser 536 67 1980
9 Lewis P J Boylan, P Friedman L A Hensby C N & Downing I Br Med J 1 1581-1582 1980
10 Von Lossonczy T O Ruiter A B- Shoute H C Van Gent C M & H[illegible] Am J Clin Nutr 31 40-46 1978
11 Moncada S & Vane J R Br Med B [illegible] 1978
12 Nordoy A Svensson B Wiebe D & H[illegible] Circ Res 43 527-534 1978
13 Remuzzi G Marchesi D Mecca, G M[illegible] Rossi E. Donati M B & de Gaetano G 2 310 1980
14 Remuzzi G Misiani R Marchesi P, L Mecca, G de Gaetano G & Donati M B 2 871-872, 1978
15 Sanders T A B & Naismith D J Lan[illegible] 655 1980
16 Siess W Scherer B Bohlig, B Roth [illegible] mann L & Weber P C Lancet I [illegible]
17 Silberbauer K Schernthaner G., Sin[illegible] Piza-Katzer H & Winter M N Eng[illegible] 300 366-367 1979
18 Sinzinger H Feigl W & Silberbauer K 2 469 1979
19 Taylor T G Gibney M J & Morgan J B 2 1378 1979
20 Webster J Rees A J Lewis P J & H[illegible] N Br Med J 2 271 1980

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LETTER TO THE EDITOR

The Lipid Hypothesis

(With apologies to W Shakespeare)

Friends clinicians colleagues lend me your eyes
I come to bury the Lipid Hypothesis not to praise it
The errors that men publish live after them
The good is oft interred with their bones
So let it be with lipids The noble Werko (8)
Hath told you the Lipid Hypothesis was false
If it were so it was a grievous fault
And grievously hath lipids answer d it
Here under leave of Werko and the rest
(For Werko is an honourable man
So are McMichael (6) and Mann (5) honourable men)
Come I to speak in the Lipid Hypothesis funeral
It was Malmros (4) belief logical and acceptable to me
But They say it was specious
And They are honourable men
Lipids brought forth support from industry
Whose funds did some research coffers fill
Did this make lipidologists ambitious?
When hypercholesterolaemics have died young we have wept
Ambition should be made of sterner stuff
Yet They say we were ambitious
And They are honourable men
You all did see that the American Heart Association
Thrice issued reports on diet and a fourth (1)
Which Oster (7) did refute Was this ambition?
Yet They say it was ambitious
And sure They are honourable men
I speak *not to disprove what They wrote*
But here I am to write what I do know
Many of you did hold it once not without cause
What cause withholds you then to mourn for it?
O judgement thou art hard on epidemiology (3)
While nutritionists seemingly have lost their reason (2)' — Bear with me
My heart is in the coffin there with the Lipid Hypothesis
And atheroma must regress before it come back to life

Gilbert Thompson MRC Lipid Metabolism Unit
Hammersmith Hospital London England

REFERENCES

1 AHA Nutrition Committee Diet and coronary heart disease Circulation 58 (Suppl) 1978
2 Food and Nutrition Board Towards healthful diets National Academy of Sciences 1980
3 Keys A Coronary heart disease serum cholesterol and the diet Acta Med Scand 207 153 1980
4 Malmros H Diet lipids and atherosclerosis Acta Med Scand 207 145 1980
5 Mann G V Current concepts Diet heart era N Engl J Med 297 644 1977
6 McMichael J Letter to the Editor A ta S 207 151 1980
7 Oster K A Duplicity in a Committee Repo and Coronary Heart Disease Am Heart J 99
8 Werkö L Diet lipids and heart attacks Scand 206 435 1979

BOOK REVIEWS

Vitamin D—Metabolism and Function By H F DeLuca DM 29 - US $16 00 Springer Verlag Berlin Heidelberg and New York 1979

The last decade has brought a wealth of information on vitamin D and its role as a prohormone is now firmly established One of the foremost investigators in this field Dr Hector F DeLuca has written a comprehensive monograph on the metabolism and function of vitamin D *as it is currently understood*

In his introduction the author states that the monograph could be looked upon as a progress report of a study of the metabolism and function of vitamin D " True to this statement DeLuca in his authoritative overview re peatedly reveals that although a lot is known there is still a lot more to be known concerning vitamin D This is especially true regarding the regulation of the metabolism of vitamin D and the role of the various metabolites in the complex homeostasis of calcium and phosphate

After a short well written historical introduction the D vitamins and their precursors are presented before the author thoroughly discusses the metabolism of vitamin D and the regulation of this metabolism with special em phasis on the kidney as an endocrine organ The reader is then given insight into the function of vitamin D in the intestine bone and kidney Analogs of vitamin D metabolites and the use of vitamin D compounds in clinical medicine are discussed

The text is easy to read and the author provides a broad and comprehensive perspective of this rapidly expanding field and gives access to a large literature

Although much of this book is too specialized for most practitioners of medicine it should be of considerable interest and value to those with special interests in the field

Lars Tejler and *John Fredrik Dymling*

Renal calculus By L N Pyrah DM 89 L Springer Verlag Berlin Heidelberg and New Y

Professor Leslie N Pyrah distinguished clinici searcher has written a monograph that covers field of renal calculous disease The author s as a urologist and researcher in a department b cerned with the investigation of calculous disor fies him to discuss the issue from a broad point

The volume contains 17 chapters dea demiological pathological biochemical medic gical aspects of the often encountered pr stones in the urinary tract It is written from standpoint and reflects the author s extensive experience

The illustrations are good the pages are wel and the print is easy to read References a plentiful are conveniently located at the end of ter A detailed list of contents the use of subhe an excellent index make it easy for the reader to he is looking for

According to the author the increase in available in recent years has necessitated an a presentation of the subject The reader howev *fail to be impressed by the wealth of informa* tific as well as clinical contained in this vol strongly recommended to internists rep urologists and everyone else interested in t medicine

Lars Tejler and J hn Fre 'rl I

Acta Med Scand 208 343–348 1980

Sinus Node Dysfunction in 128 Patients

A Retrospective Study with Follow up

E Simonsen J Stræde Nielsen and B Lyager Nielsen

From Department of Medicine B Odense University Hospital Odense Denmark

RACT A retrospective study covering all ad ns during a 6-year period revealed 128 patients sinus node dysfunction (SND) The patients were ed according to the ECG criteria chosen group tients with sinus bradycardia group II 37 with nal block/sinus arrest group III 58 with tachy syndrome Additional heart disease minantly ischaemic was found in 56% The ency and severity of symptoms increased from I to group III Pacemaker treatment was given of the cases while medical treatment alone ccessful in 17% A follow up including 104 ts was carried out after a mean observation of approximately three years Sixteen patients ied The cause of death may have been SND in only one case Five patients died of apoplec sults or complications to such In total, nine le or proven systemic embolic events were all occurring in patients with brady tachy ome A progression of the ECG abnormality a lower to a higher group took place in nine ts during the observation period It is con that SND is a condition with a broad clinical um and a stationary or slowly progressive In general, it carries a good prognosis A sub- number of deaths or disabilities in patients brady-tachy syndrome may be ascribed to ic embolism Long term anticoagulant therapy posed in this subgroup of patients with SND

ords sinus node dysfunction syncopal attacks ker treatment systemic embolism

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reasing number of publications on sinus node ction (SND) have appeared during the last e the main objects of interest being elec ysiological phenomena (2 3 8) and the possi of treatment (12 15 17) The syndrome is accompanied by symptoms varying considerably in severity There are only a few reports regarding the clinical spectrum (7 15 16) and these include smal ler numbers of patients

A study of 128 patients is presented in an attempt at defining the difference between patient groups obtained from ECG criteria with regard to the oc currence of symptoms need of treatment risk of progression and prognosis

PATIENTS AND METHODS

The study comprises 128 patients (74 men and 54 women) selected retrospectively by means of a survey of the case reports of all admissions to Medical Department B Odense University Hospital from April 1 1972 to Dec 31 1977 Telemetry but not Holter technique was employed in detection of arrhythmia and in evaluation of antiar rhythmic therapy The patients were selected on the basis of ECG findings in accordance with the criteria mentioned below Excluded from the study were patients with acute myocardial infarction or SND caused by antiarrhythmic treatment

The patient series was divided into three groups on the basis of the following ECG criteria *Group I* Persistent and in other respects unexplainable sinus bradycardia with a heart rate of less than 50/m at rest *Group II* Sinus rhythm with episodes of sinoatrial block or sinus arrest *Group III* Patients with characteristics as above and at tacks of supraventricular tachyarrhythmia (brady tachy syndrome)

A follow up examination was carried out by one of us (E S) in Sept–Oct 1978 after an average observation time of about 3 years The follow up included an interview regarding symptoms treatment and complicating dis eases clinical examination a one minute ECG and a chest X ray The information thus obtained was supplemented by existing material from admissions to our or other de partments during the period under observation

The χ^2 test was employed for the statistical analysis A significance level of 0 05 was chosen

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Abbreviations SND = sinus node dysfunction ECG = electrocardiogram

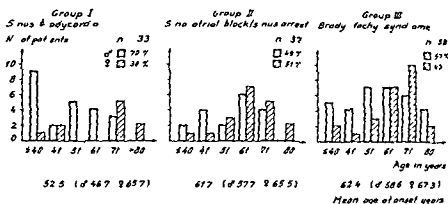


Fig 1 Distribution
age and ECG criter
128 patients at the
onset of symptoms

RESULTS

Fig 1 shows the age at the time of the onset of symptoms or signs for men and women in the three groups All age groups were represented The male female ratio was almost 1 1 in groups II and III while males predominated in group I due to an accumulation of younger men

The average age at the time of onset was highest in women and similar in all three groups A bimodal distribution was seen for men in group I which produced a lower average age at the onset than in groups II and III

The symptoms lasted for up to 40 years longest in group III Patients with symptoms of only a few days duration resulting in hospitalization were however found in all groups

Heart disease was demonstrated in two thirds of the patients (Table I) Ischaemic heart disease was most frequently seen and diagnosed in 56% of all patients Further it occurred with a significantly higher frequency in group III than in groups I and II Conduction disturbances other than SND were noted in one third of the patients Only first degree AV block (15 patients) and left anterior hemiblock (27 patients) were of quantitative importance

Like in earlier investigations cerebral symptoms (syncope dizziness) were the main causes of hospitalization (Table II) Four patients were free from symptoms A considerable number of patients in group III complained of attacks of palpitation or tachycardia Congestive heart failure was not the major problem in any case The frequency of cerebral symptoms increased from group I to grop III but the difference is not statistically significant Almost all attacks of syncope in group I were of brief duration and rare whereas they were more frequent and prolonged in the other two groups

Medical treatment was attempted in all
with symptoms due to SND In cases of br
dia and block atropine and isoprenaline w
ministered while digoxin often in comb
with quinidine and/or β receptor blocking
was given in cases of tachycardia Howeve
cal treatment alone was successful in a few
only (Table II) Thus only nine of 44 pa
group III did well on medical treatment Pac
therapy was given in cases with severe sy
when medical treatment had failed This
case in one patient in group I in 38% of the
in group II and 62% in group III

Table I *Heart disease and associated con disturbances in the three groups of pat SND*

LAH = left anterior hemiblock RBBB = righ branch block LBBB = left bundle branch block

	Group I		Group II		Group III	
	n	%	n	%	n	%
Heart disease						
Ischaemic	14	42	18	49	40	69
Rheumatic					[illegible]	
Hypertensive	3		2		3	
No heart disease	16		17		13	
Associated conduction disturbances						
1st degree AV block	5		3		7	
2nd degree AV block					1	
LAH	4		11		1[illegible]	
LBBB			1		[illegible]	
RBBB			3		1	
RBBB+LAH	3		1		4	
No conduction disturbances	22		22		37	

...II *Symptoms and treatment in 128 patients with SND*

...symptoms when admitted to hospital and treatment when dismissed B = symptoms and treatment at follow up ...act confidence limits ($p<0.05$) are indicated in parentheses

	Group I				Group II				Group III			
	A (n=33)		B (n=29)		A (n=37)		B (n=31)		A (n=58)		B (n 44)	
...ms												
...opal attacks	11	33% (18–52)	4	14% (4–32)	17	45% (29–62)	1[a]	(0–17)	34	59% (45–71)	4[a]	9% (3–22)
...ness	12	36% (?1–55)	12	41% (24–61)	24	63% (47–80)	14	45% (27–64)	33	57% (43–70)	10[a]	23% (11–38)
...ng of fast or ...eady heart												
...nty	6		7		4		7		15		16	
...s	16		2		11		2		10		3	
...			10	35%	1		10	32%	3		15	34%
...ent												
...maker	1		2		14		13	1[b]	36	6[b]	28	19[b]
...	7		6		6		4		9		7	
...	25	76%	21	72%	17	46%	14	45%	13	22%	9	21%

...01 compared to results in column A
...f patients also treated with drugs

...up

...patients died and eight absented themselves ...e follow up examination thus including 104 ...s (Table III) The average period of obser... was approximately three years but in 10% ...cases 9–12 months only

...s of SND in addition to sinus bradycardia ...oted in six patients originally belonging to ... Two patients showed episodes of sinoatrial and four had developed supraventricular ...ardia (three atrial fibrillation one paroxys... ...chycardia the character of which could not ...rmined)

...roup II three patients showed a changed ... (one atrial fibrillation two paroxysmal ...ardia)

...e were nine cases of probable or proven ...embolism Eight patients had had a stroke ...dden onset five of them had died One pa... ...ad an embolus in the femoral artery pre... by atrial fibrillation These nine patients had ...tachy syndrome

...*of death*

...the 16 deaths occurred in group II during the ...y admission (autopsy findings amyloidosis ...heart pulmonary embolism) Table IV shows ...uses of death and the autopsy findings in the ...ents who died during the period of observa... ...acemaker dysfunction was not observed

In one case a 55 year old man death could have been caused by SND He had had severe angina pectoris and brady tachy syndrome as well as earlier attacks of syncopes He died suddenly without prior symptoms of myocardial infarction Autopsy was not carried out

Symptoms and treatment

Approximately one third of the patients were free from symptoms at the follow up examination (Table II) Sixteen of these were treated with a pacemaker

Table III *Follow up examination in 104 patients with SND*

	Group		
	I	II	III
No of pats	29	31	44
No of deaths	1	5	10
No of drop-outs	3	1	4
Mean age (y)	57	64	68
Observation period (months)			
Mean	39	34	29
Range	9–95	9–68	9–64
No of pats with progressive SND	6	3	
No of pats with possible systemic embolism	1	0	8
No of pats treated for congestive heart failure	5 (17%)	7 (23%)	15 (34%)

Table IV *Deaths during the observation period*

	Sex	Age (y)	Months between discharge and death	Pacemaker treatment	Cause of death	Autopsy performed
Group I	♀	86	6		Pneumonia	
Group II	♂	64	26	+	Brain tumour	+
	♂	81	22	+	Bleeding peptic ulcer	
	♀	89	18		Pulmonary embolism	+
Group III	♂	78	10	+	Respiratory failure due to chronic bronchitis	+
	♂	84	13	+	Congestive heart failure recent MI	
	♂	62	50		Brain abscess?	
	♀	81	4		Pneumonia cerebral apoplexy	
	♀	85	17	+	Pulmonary embolism cerebral apoplexy	+
	♂	55	3		Cardiac arrest (asystole?)	
	♀	86	34	+	Pneumonia cerebral apoplexy	+
	♀	71	11	+	Gangrene of the intestine	+ (not e
	♂	69	16		Pulmonary embolism cerebral apoplexy	+
	♂	72	8		Cerebral apoplexy	

Nine patients had syncopes during the observation period One of these had a pacemaker there were no signs of pacemaker dysfunction but a severe cerebral arteriosclerosis to which the symptoms were attributed Also in five others the syncopes were considered to have been caused by a cerebral disease (epilepsy in one cerebral arteriosclerosis in four) One patient with syncopes due to SND had been prescribed a pacemaker but this kind of treatment had not been given In the remaining two patients with syncopes during the observation period the follow up revealed SND as the cause This relationship had been overlooked during the primary admission In both patients the syncopes ceased after pacemaker implantation

In 11 patients not treated with pacemaker during the primary admission despite a history of syncopes no such attacks occurred during the observation period

Table II shows that supplementary antiarrhythmic treatment had been necessary during the observation period in the majority of patients treated with a pacemaker in group III The number of patients who managed without treatment was unchanged in all three groups

DISCUSSION

The diagnostic criteria for SND have varied somewhat in the literature Ferrer (7) suggested a division into six groups based on ECG criteria Included in these were patients with chron[...] fibrillation and cases with prolonged as[...] bradycardia after DC conversion These tw[...] are not considered in our investigation as the[...] of necessity include patients who do not su[...] SND as defined today The remaining f[...] correspond to our groups I and II Howe[...] brady tachy syndrome has now been recog[...] a characteristic manifestation of SND Th[...] we have employed the criteria of Rubens[...] (16) Although based on easily recognized cl[...] teria this grouping gives a clinically impor[...] tinction between types of bradycardia and t[...] dy tachy syndrome in contrast to electro[...] logical criteria the use of which is not g[...] accepted (3 11 14)

Only a few reports covering SND in ex[...] patient series have been published S[...] occurred in 70% of the 51 patients repo[...] Rokseth and Hatle (15) and of those 71 repor[...] Rasmussen (13) as there were relatively m[...] tients with brady tachy syndrome Pacemaker[...] ment was employed in 45 and 81% respec[...] Eraut and Shaw (5) described 46 patients of[...] half had disturbances of consciousness Th[...] jority of these patients had sinus bradycard[...] pacemaker treatment was given in one case o[...] direct comparison between our patients and[...] mentioned is therefore impossible due to the[...] ences in composition

In the study of 56 patients reported by R[...]

al (16) there are certain similarities to the investigation This applies in particular to up n of the patients and the occurrence ope (45 and 48% respectively) The female ratio is almost 1 1 in the majority of re Rubenstein et al found a slight predomi f women while the present work includes en This can be attributed to an accumula ounger men with sinus bradycardia which s an apparent bimodal distribution of the onset in group I The work of Rubenstein uggests the same and thus the question hether these younger men differ from the s a whole i e in actual fact do not suffer ID

ispersion with regard to the time of onset is able but the average age at the time of r women was similar in all groups and fur men in groups II and III (Fig 1) This does port the assumption that the progression ure bradycardia to a brady tachy syndrome mon phenomenon as the average age at p was almost the same in all three groups r such a course is known and has been rated in nine of our patients (Table III) at the time of onset was on the whole nately ten years higher in women than in aspect which is somewhat similar to the nset for ischaemic heart disease

etiology of SND is unknown and different may be of importance Hereditary occur s been reported with manifestation already hildhood or early youth (9) One third of our had no signs of other heart disease Ischae rt disease was demonstrated in more than f of the patients while considerably lower ies were found in earlier publications 35% 14% (15) The fact that SND can occur m myocardial infarction seems to show that a may be a factor of importance Ischaemic ease was demonstrated significantly more tly among our patients in group III than in and II This rises the question as to wheth tachycardias in this group originate from c parts of the atrium *However patho-ana nd angiographic* investigations do not com agree on this point (4 10)

on of our patients had a pacemaker Pace treatment was not considered indicated in 13 even though they had suffered from at f syncope All but two patients were free from such attacks during the period of observation Their syncopes subsided after pacemaker implantation Thus these two patients have possibly been the object of erroneous primary evaluation It should in addition be mentioned that asystolia caused by SND may have been the cause of death in one case but sudden death (ventricular fibrillation) due to ischaemic heart disease is the most likely explanation

It may be concluded that the routine programme of the department has functioned effectively This includes telemetric observation during hospitalization and a documented relationship between the symptoms and SND prior to the decision to implant a pacemaker However prolonged observation is necessary in a number of patients as the symptoms are often intermittent and for this reason ambulatory monitoring using the technique of *Holter must be considered advantageous (14)*

On the basis of the present investigation it is impossible to determine whether pacemaker treatment has been employed too frequently Pacemaker treatment has been given in other investigations with a similar frequency provided correction is made for the difference in the composition of the patient series

The follow up examination has shown that supplementary antiarrhythmic treatment within a few years after implantation of a pacemaker is required in the majority of patients in group III This should be borne in mind during the control examination following pacemaker implantation

Nine cases of possible systemic embolism were observed during the observation time of approximately three years In eight cases this took the form of a stroke and five were fatal All of these patients had brady tachy syndrome This is in agreement with previous investigations (1 6 12) None of our patients were on anticoagulant therapy However it could be an important aid in reducing the fatalities as one half of the deaths in group III were caused by apoplectic insults or complications to such Apart from the increased frequency of embolic phenomena in group III SND appears in general *to have a good prognosis when the usual treatment* is given Several patients had recurring attacks of syncope for some years without any sequelae So the prognosis for untreated patients with syncopes due to SND seems to be much better than for untreated patients with syncopes due to atrioventricular block

ACKNOWLEDGEMENT

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REFERENCES

1 Bathen J Sparr S & Rokseth R Embolism in sinoatrial disease Acta Med Scand 203 7 1978
2 Benditt D G Strauss H C Scheinman M M Behar V S & Wallace A G Analysis of secondary pauses following termination of rapid atrial pacing in man Circulation 54 436 1976
3 Dhingra R C Amat y Leon F Wyndham C Deedwania P C Wu D Denes P & Rosen K M Clinical significance of prolonged sinoatrial conduction time Circulation 55 8 1977
4 Engel T R Meister S G Feitosa G S Fischer H A & Frankl W S Appraisal of sinus node artery disease Circulation 52 286 1975
5 Eraut D & Shaw D B Sinus bradycardia Br Heart J 33 742 1971
6 Fairfax A J Lambert C D & Leatham A Systemic embolism in chronic sinoatrial disorder N Engl J Med 295 190 1976
7 Ferrer M I The sick sinus syndrome Circulation 47 635 1973
8 Holden W McAnulty J H & Rahimtoola S H Characterisation of heart rate response to exercise in the sick sinus syndrome Br Heart J 40 923 1978
9 Lehmann H & Klein U E Familial [illegible] dysfunction with autosomal dominant [illegible] Heart J 40 1314 1978
10 Lippestad C T & Marton P F [illegible] proximal right coronary artery occlusion [illegible] 74 551 1967
11 Narula O S Samet P & Javier R P [illegible] of the sinus node recovery time Circulation [illegible] 1972
12 Radford D J & Julian D G Sick sinus [illegible] Experience of a cardiac pacemaker clinic [illegible] J 3 504 1974
13 Rasmussen K Chronic sinoatrial heart [illegible] Heart J 81 1 1971
14 Reiffel J A Bigger J T Cramer M & [illegible] S Ability of Holter electrocardiographic [illegible] and atrial stimulation to detect sinus node [illegible] tion in symptomatic and asymptomatic [illegible] sinus bradycardia Am J Cardiol 40 189 [illegible]
15 Rokseth R & Hatle L Prospective study [illegible] occurrence and management of chronic [illegible] ease with follow up Br Heart J [illegible]
16 Rubenstein J J Schulman C L Yurchak [illegible] DeSanctis R W Clinical spectrum of the sick [illegible] syndrome Circulation 46 5 1972
17 Sigurd B Jensen G Meibom J & [illegible] Adams Stokes syndrome caused by sinoatrial [illegible] Br Heart J 35 1002 1973

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The Diagnosis of Atrial Myxomas

Difficulties and Pitfalls

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[illegible]RACT Altogether seven patients with the [illegible]rative diagnosis of atrial myxoma were admit[illegible] our hospital in 1968–78 and referred for sur[illegible] In two patients no tumour was found at opera[illegible] In one of them the reason for the misinter[illegible]tion was severely malformed mitral leaflets In [illegible]her the contrast medium was injected into a [illegible]nary vein which caused a contrast defect due [illegible]dequate mixing

[illegible]ords myxoma diagnosis

[illegible]ed Scand 208 349 1980

[illegible]ma is the most common type of the rare group [illegible]mary heart tumours Three fourths of all [illegible]mas are located in the left atrium most of the [illegible]ing ones in the right (5) Since the tumour is [illegible]mon and its symptoms are variable the diag[illegible] is easily overlooked or delayed (4) Although [illegible]mas are rare it is essential that they are diag[illegible] and removed since they involve risks of seri[illegible] complications

[illegible] definite preoperative diagnosis of myxoma of [illegible]ma is established by means of echocardio[illegible] and/or cardioangiography In our experi[illegible] however these methods entail limitations [illegible]falls in some instances even leading errone[illegible] to cardiac surgery This study describes some factors behind the misinterpretation of the [illegible] angiographical and echocardiographical [illegible]s of atrial myxomas based on findings in [illegible]xoma patients

PATIENTS AND METHODS

[illegible]1968–78 seven patients with the preoperative diag[illegible] of myxoma of the atrium were referred for surgery at [illegible]s Hospital in Gothenburg Six of them had a [illegible]ted myxoma in the left atrium one in the right At [illegible]on the diagnoses were confirmed in only five patients The most important findings are summarized in the following case reports

Case I

A 26-year-old man Acutely ill with right sided paralysis ESR 12 mm Carotid angiography occlusion of the medial cerebral artery Echocardiography (Fig 1) as well as cardioangiography ten months after the onset of symptoms showed typical pictures of tumour in the left atrium extending down through the mitral valve in diastole Operation myxoma of the left atrium Mitral valve leaflets normal

Case II

A 56-year-old woman with no previous heart symptoms Gradually taken ill with frequent fever attacks often accompanied by pain in the right hypochondrium increasing tiredness and exertional dyspnoea Because of the confusing abdominal pains laparotomy was performed about one year after the onset of symptoms but only a non specific enlargement of the liver was found A few weeks later additional chest pains were noted as well as congestion of the veins of the neck and a murmur to the left of the sternum ESR 60 mm Chest X ray now showed a general enlargement of the heart The new cardiac findings led to cardioangiography disclosing a tumour of the right atrium Operation 12 months after the onset of symptoms myxoma of the right atrium

Case III

A 50-year-old previously healthy woman fallen ill with rapidly progressing tiredness and increasing dyspnoea ESR 3–6 mm Roentgenologic and auscultatory findings compatible with mitral stenosis Echocardiography and cardioangiography revealed a tumour of the left atrium partly protruding into the left ventricle in diastole Operation eight months after the onset of symptoms myxoma of the left atrium

Case IV

A 64 year-old previously healthy woman fallen acutely ill with saddle embolus Embolic specimen contained myxomatous tissue Echocardiography immediately after embolectomy was negative but a second echocardiography eight months later showed that the size of the left atrium had decreased from 4 5 to 2 8 cm but there were no echoes suggestive of myxoma. ESR 6 mm Subsequent



Fig 1 Case I Scanning from the left ventricle to the mitral valve showing classic stratified echoes of left atrial myxoma

cardioangiography however revealed a tumour of the left atrium not in contact with the mitral valve leaflets Operation eight months after the embolic incident myxoma Mitral leaflets normal

Case V

A 65 year-old woman with no previous cardiac disease During ten months increasing dyspnoea and cardiac dysfunction down to function group IV ESR 19–32 mm Auscultation and chest X ray indicative of mitral stenosis however both echocardiography and cardioangiography showed pictures typical of tumour of the left atrium partly obstructing the mitral orifice Operation ten months after the onset of symptoms myxoma Mitral leaflets normal

Case VI

A 12 year-old boy healthy until the age of seven Thereafter repeated attacks of unconsciousness sometimes in connection with ventricular extrasystoles and on one occasion transient cardiac arrest ESR 2 mm [illegible] aetiology of these attacks was unclear it was [illegible] necessary to rule out the possibility of cardiac [illegible] Echocardiography of the left atrium was abn[illegible] though the picture was not quite typical of myx[illegible] monary angiogram showed a normal left atrium [illegible] sequent contrast injection directly into the left at[illegible] sulted in contrast defects suggestive of tumour [illegible] tion normal left atrium

Case VII

A 32 year old woman with heart murmur [illegible] years Admitted because of increasing [illegible] dyspnoea ESR 26 mm Auscultation and X ray [illegible] suggested mitral stenosis Echocardiography [illegible] tumour of the left atrium (Fig 2) but cardi[illegible] did not show any contrast defects Operation [illegible] congenitally deformed and thickened mitral [illegible] atrial tumour

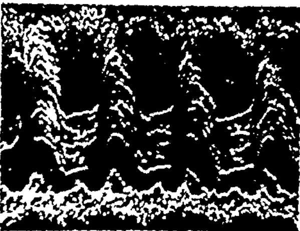


Fig 2 Case VII Polaroid photo showing parallel stratified echoes suggestive of left atrial myxoma A congenitally deformed stenotic mitral valve was however found at surgery

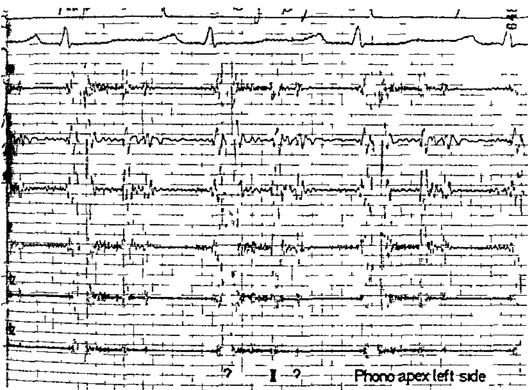
Non invasive studies of the heart including [illegible] diography pulse curves apexcardiography [illegible] diography were performed in all patients at the [illegible] ment of Clinical Physiology with the exception of [illegible] as the above methods were not yet in practice [illegible] 1968 (7)

The cardioangiographies were performed by [illegible] injection into either the right atrium or the pu[illegible] artery depending on the expected location of the [illegible] In case VI a contrast injection into the left atr[illegible] made in addition to the injection into the pu[illegible] artery

PESULTS AND DISCUSSION

Atrial myxomas were found at operation [illegible] cases—four on the left side and one on the ri[illegible] the remaining two patients one had cong[illegible] malformed stenotic mitral valves whereas [illegible] quite normal

The clinical symptoms and findings lead[illegible] further examination and surgery were [illegible]



Case III Phonocardiogram showing a very strong
st sound and a diastolic extra sound The question marks here indicate that these sounds are not typical of mitral stenosis (see Fig 4)

valvular disease in three patients (III V and
d peripheral artery emboli without any clini
vident heart disease in two (I and IV) In one
I) puzzling symptoms in combination with
eart failure were noted One patient (VI)
uncharacteristic disturbances of conscious
used by arrhythmias
one of the verified myxomas was suspected
on clinical grounds but only after symp
ad been present for ten months (case I)
ter none of the patients showed any classic
ok symptoms indicative of myxoma such as
bination of positional dyspnoea long last
acks of fever and high ESR (5) The only
with typical positional dyspnoea was the
th mitral stenosis (case VII)
most confusing clinical picture was produced
ight atrial myxoma Because of unexplained
megaly with ascites an exploratory lapa
y was performed in this case Suspicions
not directed towards the heart until the patient
ped chest pain and increasing distension of
ns of the neck The complex symptomatolo-gy of right atrium myxomas however is well known and has been described earlier (5)

In no patient was the final diagnosis made earlier than eight months after the onset of symptoms In two (III and V) suspicion of myxoma arose as a result of a routine echocardiographic examination for possible mitral stenosis The remaining two myxomas (I and IV) which presented clinically as emboli were revealed only because the source of the emboli was searched for

In three cases (I III and V) pictures typical of myxoma of the left atrium were found by non inva sive means and by angiography The characteristic picture with parallel echoes behind the mitral leaf lets was seen on echocardiography (Fig 1) These patients had also a quite clear diastolic extra sound differing from an opening snap by its unusual low frequency and which when registered together with the apex curve appeared clearly after the 0-point and sometimes even after the rapid filling wave i e too late to be an opening snap (Figs 3 and 4) All these patients also displayed a very strong and ex traordinarily late component in their first heart

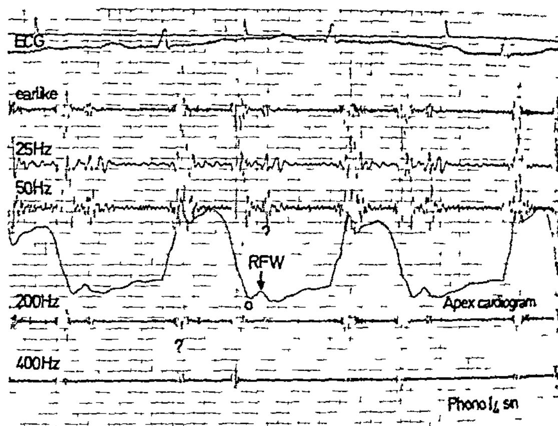


Fig 4 Case III Apexcardiography shows that the first heart sound is simultaneous with the top of the apexcardiogram and that the diastolic extra sound comes later than the rapid filling wave (*RFW*) These time relations exclude the possibility of mitral stenosis and suggest the sounds are produced by atrial myxoma, probably the sudden arrest in the swinging movement

sound far too late to be a normal mitral closing sound and probably like the early diastolic extra sound produced by movements of the myxoma (Figs 3 and 4) (1 2)

Echocardiography immediately after the embolic episode was negative in *case IV*. At repeated examination eight months later the size of the left atrium had decreased from 4 5 to 2 8 cm Whether this reduction in atrial size was due to regeneration of a myxomatous tumour or a technical error could not be decided The absence of echocardiographic findings typical of myxoma may be explained by the myxoma not reaching down to the mitral valves The echo picture of *case II* in whom operation showed a malformed mitral valve could not be differentiated from that of a left atrial myxoma (Fig 2) However at the time of these examinations (cases IV and VII) the echoes were registered by means of polaroid photos from a storage oscilloscope Later technical developments such as gray scale recording and scanning have improved the diagnostic accuracy of echocardiography considerably (Fig 1) Nevertheless the extra sound occurring at the place of an ordinary opening would have made us more reluctant to a diagnosis of myxoma in case VII (see also diffuse immobile unstratified cloud of echoes the left atrium i e findings not typical of could be registered in case VI by means of a chart recorder as well as by two-dimensional element echocardiography However the very serious history of this patient and cardiac arrest additional ca was considered necessary

Since 1978 we include two-dimensional scan echocardiography in our non-invasive investigations This technique is superior in det masses in the heart and probably would the diagnostic problems in cases IV VII

All patients with surgical verified were correctly diagnosed by means of In patient VII with severely malformed

where the echo picture suggested myxoma the graphy was negative with regard to tumour only angiographically misinterpreted case the left atrium appeared normal at pulmonary graphy At an additional contrast injection the left atrium the tip of the catheter was accidentally placed in a pulmonary vein which likely contributed to the appearance of a filling in the atrium erroneously interpreted as a At operation the left atrium was normal Retrospectively it appears that the angiographical observed contrast defect must have been caused by inadequate mixing of contrast medium in atrium due to the position of the catheter (6) correct diagnosis would have been avoided if injection had been made directly into the left or only a pulmonary angiography had been Thus when a tumour in the left atrium suspected a contrast injection into the pulmonary artery is the method of choice It is advisable the cinetechnique since this often allows the demonstration of the typical movements of the myxoma as opposed to mural thrombi (5)

CONCLUSIONS

There is no clinical picture which can be regarded typical of atrial myxoma The clinical findings ... primarily raise suspicions of myxoma those of mitral stenosis often with remarkably ... progression and second peripheral emboli ... in young and otherwise healthy individu...

Echocardiography must be performed in all cases of suspected mitral stenosis since echocardiography combined with phonocardiography and apexcardiography will give a conclusive diagnosis of all myxomas causing obstruction of the mitral valves (1 2) Confirming angiography should be unnecessary in such cases Echocardiographic findings that are difficult to interpret and cases of negative echocardiograms should when the clinical evidence is strongly suggestive of myxoma be followed by angiography Surgically removed peripheral emboli must be examined microscopically for myxomatous tissue

Myxoma is a rare cause of arterial embolization All patients with this symptom cannot be examined with regard to cardiac tumour However an unexplained peripheral embolus in a young person should suggest myxoma (5) Since echocardiography and probably angiography immediately after an embolization may give negative results (case IV) such examinations should be repeated after 6–12 months in cases with clinical findings strongly suggestive of myxoma (3)

REFERENCES

1. Becker L C & Conti C R Left atrial myxoma Evidence of tumour movement by apexcardiogram Chest 60 280 1971
2. Craige E & Algary W P Left atrial myxoma Diagnosis *with the help of the phonocardiogram and apex* cardiogram Arch Intern Med 129 470 1972
3. Croxon R S Jewitt D Bentall H H Cleland W P Kristiansson A & Goodwin J F Long term follow up of atrial myxoma Br Heart J 34 1018 1972
4. Goodwin J F Stanfield C A Steiner R E Bentall H H Sayed H M Bloom V R & Bishop M B Clinical features of left atrial myxoma Thorax 17 91 1962
5. Greenwood W F Profile of atrial myxoma Am J Cardiol 21 367 1968
6. Steiner R F Radiologic aspects of cardiac tumours *Am J Cardiol 21* 344 1968
7. Waagstein F Hjalmarsson Å Varnauskas E & Wallentin I Effect of chronic beta adrenergic receptor blockade in congestive cardiomyopathy Br Heart J 37 1072 1975

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The Clinical Impact of Long-Term ECG Recording

A Retrospective Study of 150 Patients

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ACT One hundred and fifty patients referred ECG (LECG) recording at a university were monitored for 12 hours or more. The physicians' patient records were studied 12 more after monitoring in an attempt to if and how LECG had affected patient man-. Seventeen patients were treated with per pacemakers and 13 with antiarrhythmic as a direct result of LECG. Thirteen patients erienced symptoms with concomitant cardiac mia at the time of recording were considered equire treatment. In 17 patients who experi- symptoms without concomitant arrhythmia monitoring cardiac arrhythmia could be at as the cause of the symptoms. In 9 more , LECG was considered to have contributed le clinical information (which could not ned by other diagnostic methods) to the re- physician. Thus LECG was considered to fected the referring physician's management ments in 69 cases (46 %)

ys rds arrhythmia diagnosis, arrhythmia therapy, ardiography, tape recording.

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rm ECG (LECG) monitoring using a portable recorder is a well established diagnostic cardiology (1, 3, 4). Although the applica- of this technique are manifold, two areas to dominate: 1) Follow-up of patients with rdial infarction (MI) in order to find indi- at risk of sudden cardiac death. 2) Investi- patients with symptoms possibly caused by ttent cardiac arrhythmia.

ough a relationship between severe ventricu- rhythmia and subsequent sudden death in the ll period has been demonstrated (11, 14), tter application has not attracted much atten- Sweden. The lack of evidence that treatment ventricular arrhythmia in these patients re- duces the risk of sudden death may account for the reluctant attitude of the cardiologists. The value of LECG in the management of the latter category of patients is more evident and has been demonstrated by many authors (2, 5, 7, 12). If one succeeds in recording the LECG during symptoms of the kind that the patient has complained of, cardiac arrhythmia can either be verified or excluded as the cause of the patient's complaints. In the former case therapeutic intervention (pacemaker therapy, antiarrhythmic drugs) often relieves the patient of his symptoms. In the latter case unnecessary therapy may be avoided and further investigation can be conducted to other directions. However useful clinical information can sometimes be obtained from LECG even if the patient had no symptoms at the time of recording.

In an attempt to evaluate the impact of LECG on patient management we studied 150 patients retrospectively.

STUDY POPULATION

A total of 150 consecutive patients referred from seven departments in our hospital (Table I) during the period Aug 1976–Oct 1977 were included in the study. Their mean age was 59 years. 57% were males. 90% were referred because of symptoms of possible cardiac origin (Table II). Most of the recordings were made on outpatients.

METHODS

Each patient was monitored for at least 12 hours using a portable one-channel FM cassette tape recorder (SPA Helgres). A detailed diary of activities and symptoms was required. A small number of patients were monitored for more than 12 hours, 36 hours being the maximum. Twenty-one patients were subjected to repeated monitoring periods (2 or 3 separate occasions).

Abbreviations: LECG = long-term electrocardiogram, MI = myocardial infarction.

Table I *Number of patients from the seven referring departments*

Referring department	No of pats
Cardiology	60
Internal Medicine	45
Neurology	22
Thoracic Surgery	12
Pediatric Cardiology	9
Pulmonary Medicine	1
Urology	1
Total	150

The tapes were analyzed by a computer aided method (10) We studied the referring departments patient records and our diagnostic reports 12 months or more after the recording in an attempt to establish if and how LECG had affected the management of the patients To that end each patient was assigned to one of the following six categories 1) The LECG led to implantation of a permanent pacemaker 2) The LECG led to initiation of or change in antiarrhythmic drug therapy 3) Arrhythmia was found on the LECG during periods of relevant symptoms but the patient received no treatment as a result of the findings (The findings at LECG were nevertheless regarded as valuable since a diagnosis could be made) 4) No arrhythmia was found during periods of relevant symptoms cardiac arrhythmia could therefore be excluded as the cause of the patient s complaints 5) Other cases in which the result of LECG information was judged to be valuable for the referring physician 6) No evidence that the result of LECG provided valuable information to the referring physician

RESULTS

Out of the 150 patients under study 135 were referred because of symptoms which might be due to cardiac arrhythmia (Table II) Relevant symptoms [illegible]ing the time of recording were experienced by 54 [illegible] them LECG was conclusive in 44 of these pa[illegible] cardiac arrhythmia could either be verified (27 patients) or excluded (17 patients) as the cause of the symptoms In 10 patients there was a doubtful relationship between reported symptoms and detected arrhythmia

Altogether 69 patients (46%) 44 of them with relevant symptoms during LECG and 25 without such symptoms were considered to belong to categories 1–5 in which LECG to some extent contributed to patient management (Table III)

Pacemaker therapy

A permanent pacemaker was implanted in 17 patients as a direct result of LECG in 15 due to sinus node dysfunction in 2 due to a [illegible] conduction defects Six of these 17 pa[illegible] enced symptoms during the monitored [illegible] bradycardia

Antiarrhythmic drug therapy

Antiarrhythmic drugs were administered [illegible] tients as a direct result of findings of ta[illegible] mia on the LECG Eight of these 13 pa[illegible] enced symptoms during the monitored [illegible] tachyarrhythmia Six of these patie[illegible] digitalis three verapamil two β-block[illegible] one quinidine and one procainamide

Symptoms and arrhythmia but no trea[illegible]

Altogether 27 patients had cardiac ar[illegible] ing symptoms In 13 of them no trea[illegible] instituted as a result of the findings [illegible] 13 patients had a subjective feeling of [illegible] rhythmia The objective finding of [illegible] rhythmia as the cause of the sympt[illegible] sidered to have a reassuring influence [illegible] them and the findings at LECG we[illegible] considered useful

Symptoms but no arrhythmia

Seventeen patients experienced symp[illegible] concomitant arrhythmia during LECG [illegible] vestigation led to a neurological diagno[illegible] tients In 3 patients a psychogenic cause [illegible] ered likely In the remaining 9 patients the [illegible] the symptoms was still unknown at the [illegible] follow up

Table II *Main indication for LECG re[illegible] 150 non selected patients*

Indication	N[illegible]
Patient suffers from symptoms which m[illegible] be due to cardiac arrhythmia	[illegible]
Syncope	[illegible]
Dizziness "feeling faint"	[illegible]
Palpitations irregular heart rhythm [illegible]	[illegible]
Chest pain	[illegible]
Other symptoms	
Patient does not suffer from any sym[illegible]	
Check-up of frequency an[illegible] severity or arrhythmia already by resting ECG	
Total	

study points to the value of analyzing also the tapes from patients without symptoms during the time of recording

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REFERENCES

1 Chung E K Ambulatory electrocardiography Springer Verlag New York 1979
2 van Durme J P Tachyarrhythmias and transient cerebral ischemic attacks *Am Heart J (Annotations)* 89 538 1975
3 Fletcher G F Dynamic electrocardiographic recording *Futura Publishing Co Mount Kisco 1979*
4 Harrison D C Fitzgerald J W & Winkle R A Ambulatory electrocardiography for diagnosis and treatment of cardiac arrhythmias N Engl J Med 294 373 1976
5 Johansson B W Long term ECG in ambulatory clinical practice Eur J Cardiol 5 39 1977
6 Kennedy H L Underhill S J & Warbasse J R Practical advantages of two-channel electrocardiographic Holter recordings Am Heart J 91 822 1976
7 Lipski J Cohen L Espinoza J [illegible] S & Donoso E Value of Holter [illegible] sessing cardiac arrhythmias in [illegible] Am J Cardiol 37 10[illegible] 1976
8 Lopes M G Runge P [illegible] Schroeder J S Comparison of [illegible] ambulatory ECG monitoring Chest [illegible]
9 McLeod A A & Jewitt D E [illegible] ambulatory electrocardiographic [illegible] eral hospital Br Med J 1 1197 197[illegible]
10 Pahlm O Borjesson P O Joha[illegible] B Petersson K Sornmo L & We[illegible] cient data compression and arrhy[illegible] long term ECGs In Proceed[illegible] Cardiology 1978, pp 395-3[illegible] IEE 78CH1391 2C Long Beach 1978
11 Rehnqvist N & Sjogren A [illegible] prior to discharge and one year after [illegible] infarction Eur J Cardiol 5 425 197[illegible]
12 Schott G D McLeod A A & Je[illegible] diac arrhythmias that masquerade [illegible] Med J 1 1454 1977
13 Tzivoni D & Stern S Pacemake[illegible] based on ambulatory ECG mon[illegible] cerebral symptoms Chest 6[illegible] 2[illegible]
14 Vismara L A Amsterdam E A & [illegible] Relation of ventricular arrhythmias [illegible] phase of acute myocardial infarction [illegible] after hospital discharge Am J Med [illegible]

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[Th]e Outcome of Patients with Transient Ischemic Attacks and Stroke Treated with Anticoagulants

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CT Long term anticoagulant treatment n to 25 patients with transient ischemic TIA) and 49 stroke patients with reversible neurolog cal deficit or cerebral embolism 16 TIA patients were observed without anti Life table analyses, comparing ved w th the expected frequency revealed mortal ty in the TIA patients irrespective er or not they had received anticoagu e stroke patients treated with anticoagulants a higher mortality than expected On the nd the incidence of subsequent stroke was r than expected in the TIA and stroke pa ated with anticoagulants, while it was signifi creased in the TIA patients not treated with lants Thus the risk of stroke but not the eath was normalized by the anticoagulant t Unacceptably serious bleeding complica e seen in the group of stroke patients with lant treatment Bleeding complications in and stroke patients seemed to be related y treatment high blood pressure on admis- insufficient pat ent compliance

ls anticoagulant treatment trans ent schem c troke compl cat ons

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ulant treatment for the prevention of ca ry insuff c ency was first reported by Milli in 1955 (16) S nce then alternative anti c treatment w th ant platelet aggregating as been presented (8) Though definite lack ng on the protective role of all these 6 9) ant coagulants are st ll recommended ed pat ents with trans ent ischem c attacks l) progressing stroke or embolism of origin (10 13 22)

g a prospect ve ep demiological survey of d s roke ant coagulant treatment was according to the recommendations issued by the Joint Committee for Stroke Fac l ties in 1973 (18) The present report deals with the influence of the therapy on the survival time and fre quency of new cerebrovascular symptoms in these patients The side effects observed during antico- agulant treatment are also reported

PATIENTS AND METHODS

The pat ents are the 74 who received ant coagulant treat ment during a 4-year ep dem ological study of TIA and stroke n the commun ty of Soderhamn start ng in 1975 The method for trac ng and registrat on has been reported elsewhere (20) Forty four pat ents w th debut ng TIA were reg stered 8 of them were cons dered to have no general contraind cat ons for anticoagulant therapy Three of these pat ents underwent neck vessel surgery and were excluded leaving 25 pat ents n the TIA ant coagulant group The remain ng 16 TIA pat ents rece ved the standard therapy given to all pat ents when necessary for d seases other than cerebrovascular but no ant platelet aggregat ng agents or vasod latators were adm n stered

Fourty n ne pat ents with stroke were treated w th anticoagulants They were a m nority of the 81 patients who had their first stroke during th s period TIA s de fined as rap dly developed cl n cal s gns of focal cere bral dysfunct on of presumed vascular origin not lasting more than 24 hours Drop attacks or vert go w thout any other symptoms as well as migraine w th assoc ated neurological symptoms were not suff c ent for the d agno- s s of TIA TIA recurrence mpl es a new attack after a symptom free interval of more than 24 hours The stroke pat ents belonged to one of two categories 34 suspected of embol sation from the heart or large vessels hav ng min mal res dual symptoms and 15 w th re ers ble schemic neurological def c t (RIND) In the latter cate gory the symptoms subsequently d sappeared but after more than 24 hours

The follow ng numbers n the M nnesota code (3) were

Abbrev at ons TIA trans ent schem c attacks RIND revers ble schem c neurological def c t TT Thrombo- test® BP blood pressure

study points to the value of analyzing also the tapes from patients without symptoms during the time of recording

ACKNOWLEDGEMENTS

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REFERENCES

1 Chung E K Ambulatory electrocardiography Springer Verlag New York 1979
2 van Durme J P Tachyarrhythmias and transient cerebral ischemic attacks Am Heart J (Annotations) 89 538 1975
3 Fletcher G F Dynamic electrocardiographic recording Futura Publishing Co Mount Kisco 1979
4 Harrison D C Fitzgerald J W & Winkle R A Ambulatory electrocardiography for diagnosis and treatment of cardiac arrhythmias N Engl J Med 294 373 1976
5 Johansson B W Long term ECG in ambulatory clinical practice Eur J Cardiol 5 39 1977
6 Kennedy H L Underhill S J & Warbasse J R Practical advantages of two-channel electrocardiographic Holter recordings Am Heart J 91 8?2 1976
7 Lipski J Cohen L Espino [illegible] S & Donoso E Value of [illegible] sessing cardiac arrhythmias [illegible] Am J Cardiol 3 10 197?
8 Lopes M G Runge P [illegible] Schroeder J S Comparison of [illegible] ambulatory ECG monitoring Chest [illegible]
9 McLeod A A & Jew[illegible] D E [illegible] ambulatory electrocardiographic [illegible] eral hospital Br Med J 1 1197 197?
10 Pahlm O Borjesson P O [illegible] B Petersson K Sornmo L & [illegible] cient data compression and arrhythmia [illegible] long term ECGs In Proceedings [illegible] Cardiology 19 8 pp 395-3?? IEEE C 78CH1391 ?C Long Beach 19 8
11 Rehnqvist N & Sjogren A [illegible] prior to discharge and one year after [illegible] infarction Eur J Cardiol 5 4?5 19??
12 Schott G D McLeod A A & Je[illegible] diac arrhythmias that masquerade as [illegible] Med J 1 1454 1977
13 Tzivoni D & Stern S Pacemaker [illegible] based on ambulatory ECG monitoring [illegible] cerebral symptoms Chest 6? ? 4 197? [illegible]
14 Vismara L A Amsterdam E A & [illegible] Relation of ventricular arrhythmias [illegible] phase of acute myocardial infarction [illegible] after hospital discharge Am J Med [illegible]

d. Causes of death

Sex	Anticoagulant group	Non anticoagulant group	Stroke anticoagulant group Age (y)	Sex	
	Myocardial infarction		44	♂	Renal failure
	Gangrene		66	♂	Stroke
	Cancer		66	♂	Congestive heart failure
	Renal failure		67	♀	Stroke
		Cancer	71	♂	Stroke
		Congestive heart failure	71	♂	Stroke
		Stroke	72	♀	Intestinal hemorrhage
		Stroke	72	♂	Myocardial infarction
		Stroke	74	♂	Myocardial infarction
		Stroke	74	♀	Pneumonia
			76	♀	Septicemia
			78	♂	Myocardial infarction
			79	♀	Cancer
			81	♂	Stroke
			84	♂	Pneumonia

RESULTS

...an age and mean BP during the first week ...gistration were lower in the group of patients ...with anticoagulants than in the group receiv- ...dard therapy while no difference was found ...distribution by sex The proportion of pa ...with definite ECG changes was not signifi ...higher among those given standard therapy ...I) In the group of stroke patients treated ...anticoagulants there was a male preponder

...observed survival curves as well as the ...onding curves for the expected survival in ...oup are shown in Figs 1–3 In the interval ...ars of observation the mortality is higher ...pected in both TIA groups the change being ...significant ($p<0.05$) in the anticoagulant group (Fig 1) The cause of death was stroke related in 4 out of 6 patients in the TIA group given standard therapy while none of the 4 patients who died in the TIA anticoagulant group had suffered from a stroke (Table II) In the group of stroke patients given anticoagulant treatment the mortality was significantly increased in periods 1–2 2–3 and 3–4 years (Fig 3) Five of the 15 patients in the stroke anticoagulant group who died had recently suffered from a new stroke (Table II) Cardiovascular disease was the major cause of death in all groups

The incidence of stroke was significantly increased during the interval 2–3 years in relation to the expected rate in the group of TIA patients given standard therapy (Fig 4) On the other hand the TIA and stroke groups with anticoagulant treatment

Expected
Years since first stroke
Anticoagulant group (n 49) o–o–o

...Survival after the first symptoms in 49 stroke ...with anticoagulant treatment (O) compared to the ...ted rate in an age- and sex matched population

100
70
50
30
% Chance of living free of stroke ±2 SD
Expected
1 2 3 4
Years since first TIA
Non anticoagulant group (n 16) o–o–o

Fig 4 The chance of living free from stroke after the first symptoms in 16 patients without anticoagulant treatment (O) compared to the expected chance in an age and sex matched population

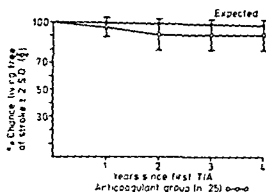


Fig 5 The chance of living free from stroke after the first symptoms in 25 TIA patients with anticoagulant treatment (O) compared to the expected chance in an age and sex matched population

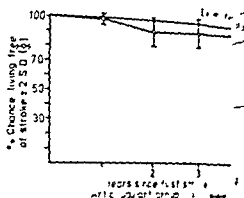


Fig 6 The chance of living free from stroke [illegible] in 49 stroke patients with anticoagulant [illegible] compared to the expected chance of living free [illegible] in an age and sex matched population

did not display any significant increase in incidence of stroke (Figs 5 and 6)

All three patients who underwent neck vessel surgery are alive and free from stroke and TIA recurrences after observation times of 19 26 and 30 months, respectively

The proportion of patients having TIA recurrence after the initiation of anticoagulant treatment was about the same as in the standard treatment group

Table III *Number of TIA patients with 1 2–4 5 or more recurrences of TIA*

	No of recurrences		
	1	*2–4*	*≥5*
Anticoagulant group (n=25)	6	2	1
Non anticoagulant group (n=16)	2	3	1

Table IV *Number of recurrent TIAs in relation to TT values in that period (n=25)*

TT value (%)	No of recurrences		
	1	2–4	≥5
<5ᵃ	–	–	–
5–15	5	1	–
>15ᵃ	–	1	–
Unstableᵇ	1	–	1

ᵃ Not within the 5–15% interval in one direction twice or more yearly
ᵇ Not within the 5–15% interval in either direction twice or more yearly

(Table III) The majority of those [illegible] TIA during anticoagulant treatment [illegible] teria for satisfactory treatment i e the TT were within the range of 5–15% during [illegible] in question (Table IV) The TT values [illegible] factorily high at least once a year in 3 of [illegible] patients in whom TIA recurred [illegible] does not differ from that in the whole [illegible] 25) One third of the TIA and stroke [illegible] TT values outside the therapeu[illegible] or more during the first year of treatment [illegible] V) The values were more stable dur[illegible] year when only 5 patients out of 60 [illegible] values twice or more

Fifteen bleeding complications occ[illegible] TIA and 11 in the stroke anticoagula[illegible] VI) making hospital care necessary [illegible] proportion in the stroke group is not [illegible] significant Nine of the complications [illegible] after 9 months of treatment [illegible]

Table V *Therapeutic control expressed [illegible] values in relation to duration of therapy [illegible]*

TT value (%)	Year of treatment			
	1st	2nd	3rd	[illegible]
5–15	49	55	13	4
<5	3	–	1	[illegible]
>15	7	–	–	[illegible]
Unstable	14	5	–	[illegible]
Total	73*	60	14	4

One patient lost for control treatment [illegible] sixth month

[Table] Complications during anticoagulant therapy in relation to age, duration of therapy, BP on [admission] (BP_a), mean BP in the first week (BP_w) and TT value

	Age (y)	Duration of therapy (mo)	BP	BP_w	TT value (%)	Outcome
[...]l hemorrhage	73	39	160/105	131/77	5–15	
[...]orrhage	63	15	150/80	134/84	Unstable	
[...]ia	63	3	140/60	147/62	5–15	
[...]eous hemorrhage	77	2	190/85	152/76	5–15	
[...]bral hemorrhage	66	9	220/105	174/95	5–15	Lethal
[...]bral hemorrhage	71	13	220/135	219/117	Unstable	Lethal
[...]bral hemorrhage	81	2	170/90	153/80	<5	Lethal
	72	2	160/120	171/92	5–15	Lethal
[...]l hemorrhage	74	34	160/120	130/89	5–15	
[...]hemorrhage	65	39	180/90	145/81	Unstable	
[...]hemorrhage	73	15	180/90	135/84	5–15	
[...]hemorrhage	73	1	210/105	120/70	5–15	
[...]hemorrhage	77	10	200/90	151/70	Unstable	
[...]orrhage	70	1	150/90	138/79	<5	
[...]taneous hemorrhage	72	32	150/90	166/95	<5	

[...]agulants were given after the BP was more adequately controlled (mean 177/97) in the second week

[...]thal outcome, 3 intracranial hemorrhages [...]testinal bleeding, all in the stroke group. [...] 3 patients with intracranial bleeding, 2 had [...] diastolic BP of 95 mmHg or more, while [...]d had TT values of less than 5% on two [...]s during the 2 months of therapy. In both [...]g[...]lant groups, 6 patients had a mean diastol[...] of 95 or more. Three of these developed [...]g complications, though the BP was lowered [...]hypertensive agents within 2 weeks. The [...]stolic BP on admission exceeded 95 in 25 of [...]ents given anticoagulants later on, of whom [...]oped bleeding complications (Table VI).

DISCUSSION

[...] study there was a selection of the patients [...] anticoagulants in both the TIA and the stroke [...]. Consequently, the patients given antico[...]nts and those given standard therapy are not [...]rable with respect to age and BP distribution. [...] table method enables one to compare the [...]ed mortality in the patient group with the [...]ted mortality in a population with the same [...]tion by age and sex (7). Obviously the mor[...] was increased in relation to the expected rate [...] patient groups receiving anticoagulants [...] is in accordance with the results of 13 other studies on the effect of anticoagulants on TIA and stroke in which no benefit was derived in terms of normalized mortality (10).

The comparison of observed and expected incidence of stroke using the same method as described above is probably more adequate as the reference figures are derived from the Soderhamn population. Thus the observed normal stroke incidence in the TIA anticoagulant group and the increased incidence in the TIA standard treatment group might represent a true reduction as a result of the anticoagulant treatment, since age differences are taken into account. The other variable that differs between these two groups is BP, though the discrepancy is rather small. Previous studies on the natural course of TIA failed to show that stroke was more likely if the patient was hypertensive (5). Thus the present small difference is probably of marginal importance. However, the present type of comparisons can just indicate, but never prove, a beneficial influence of anticoagulant treatment, as little as other types of non randomised studies (5, 6, 10). Even harder to judge are the results of studies where the observed incidence of stroke in the treatment group is compared to the incidence in the same patients after termination of therapy or to the incidence in another, untreated population (14, 17). In the former case, the almost exponentially in

creasing risk of stroke with increasing age as well as possible rebound effects of withdrawal of the drug are not taken into account In the latter respect the differences between two populations regarding the variables mentioned above including heart disease make comparisons meaningless

The patients in this study continued having TIAs during the therapy in spite of TT values mostly in the range 5–15% The literature includes some reports of ceased TIA after initiation of anticoagulant therapy as well as increased TIA incidence after withdrawal of therapy (10) In most studies the further course of TIA after anticoagulant treatment is incompletely reported

The complications of anticoagulant treatment in this study are rather harmless in the TIA group while the types of complications in the stroke group are unacceptably serious There is some controversy regarding anticoagulant treatment in patients with completed stroke Bleeding complications and even increased mortality in connection with anticoagulant treatment were reported early on (1 2 12) Other studies failed to show a long lasting therapeutic reduction of neurological symptoms It was concluded that the dangers might outweigh the benefits (4 21) The relationships between complications and BP patient compliance and duration of treatment were however not clarified In a recently published study of comparatively young patients with a mean treatment time of 11 months complications were acceptably few and harmless (14) The patients in that study were carefully selected and all were investigated with angiography and repeated lumbar punctures In the present study it is notable that 3 out of the 6 patients whose mean diastolic BP was 95 or more in the first week after admission developed bleeding complications of which two intracerebral hemorrhages were lethal This occurred despite lowering of the BP within 2 weeks during antihypertensive drug therapy While increased mean diastolic BP is unfavorable for the outcome the first diastolic BP after admission is hardly predictive Most bleeding complications occurred after 9 months of treatment and were not attributable to hypertension or insufficient patient compliance

The majority of patients with TIA or stroke seen at medical wards in Sweden are older than those who participated in most previous studies (10 14) The results of the present study comprising all patients with onset of TIA during a 3-year period and some old stroke patients [illegible] effect of anticoagulant treatment [illegible] normal incidence of stroke However [illegible] anticoagulants must be restricted [illegible] good cooperation and low mean [illegible] treatment should be confined to the period [illegible] est risk of suffering a stroke which is [illegible] after the onset of TIA (5) in view of [illegible] number of unexpected late bleed[illegible]

REFERENCES

1 Baker R N An evaluation of [illegible] in treatment of cerebrovascular disease [illegible] Veterans Administration Cooperative [illegible] Atherosclerosis Neurology Section [illegible] 132 1961
2 Baker R N Broward J A [illegible] H C C M Groch S N Heyman A [illegible] McDewitt E Scheinberg P [illegible] Toole J F Anticoagulant therapy [illegible] tion Report on Cooperative Study [illegible] 823 1962
3 Blackburn H Classification of the [illegible] for population studies Minnesota code [illegible] cardiol 2 305 1963
4 Bradshaw J & Brennan S Trial of long-term anticoagulant therapy in the treatment of [illegible] associated with a normal carotid [illegible] Neurol Neurosurg Psychiatry [illegible]
5 Brust J C M Transient ischemic [illegible] history and anticoagulation [illegible]
6 Cervantes F D & Schneiderman L J [illegible] agulants in cerebrovascular disease [illegible] 135 875 1975
7 Colton T Longitudinal studies and [illegible] life table Statistics in medicine [illegible] Brown and Co Boston 19[illegible]
8 Dyken M Assessment of the [illegible] aggregating agents in transient [illegible] stroke and death Stroke 10 604 19[illegible]
9 Editorial Preventing stroke Br M J [illegible]
10 Genton E Barnett H J M [illegible] & Hoak J C Cerebral ischemia [illegible] bosis and of antithrombotic therapy [illegible] 1977
11 Greenwood M The errors of [illegible] vivalship tables Appendix I In Reports [illegible] health and statistical subjects no 33 [illegible] Stationary Office London 1926
12 Hill A B Marshall J & [illegible] vascular disease Trial of long-term [illegible] therapy Br Med J 2 1003 19[illegible]
13 Lieberman A Hass W K [illegible] Kupersmith M Bear G & Chase R [illegible] hemorrhage and infarction in [illegible] with prosthetic heart valves [illegible]
14 Link H Lebram G Johansson [illegible] Prognosis in patients with [illegible]

al tem ory during and after ant coagulant therapy ke 10 579 1979
lan C H & McDowell R H Treatment of n sen ischem c attacks Stroke 9 299 1978
lan C H S ekert R G & Sh ck R M ides n cerebro ascular d sease The use of anti gulant drugs n the treatment of nterm ttent in ciency of the nternal carot d arterial system yo Clin Proc 30 8 1955
son J E Muller R & Bernel S Long term coagu ant therapy for TIAs and m nor strokes minimum res duum Stroke 7 444 1976
port of the Jo nt Comm ttee for Stroke Fac l t es cle 4 69 1973
ti tcal Abstract of Sweden 1975
zon A A prospect e ep dem ological survey of cerebrovascular d seases n a Swed sh commun ty Ups J Med Sci 84 235 1979
21 Thygesen P Christensen E Dyrbye M E ken M Frantzen E Gormsen J Lademann A Lennox Buchtal M Ronnov Jessen V & Therkel sen J Cerebral apoplexy A cl n cal rad olog cal electroencephalograph c and patholog cal study w th special reference to the prognos s of cerebral infarc t on and the results of long term ant coagulat on therapy Dan Med Bull 11 233 1964
22 W lson W R Geraci J E Dane lson G K Thompson R L Sp ttell J A Wash ngton J A & G ul ani E R Ant coagulant therapy and central nervous system compl cat ons in pat ents w th prosthet c valve endocard t s C rculat on 57 1004 1978

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Comparison of Energy and Nutrient Intakes in Women with High and Low Blood Pressure Levels

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RACT The present study found no link be- the intake of energy and various nutrients, on hand and high or low blood pressure (BP) in on the other Sixty women not on treatment ertension were selected from a defined popu and examined applying the duplicate portion ue with respect to the relationships between the intake of energy and nutrients They were d from above the 95th percentile for BP (group from below the 30th (group B) The two were age-matched The food sampling com- six days divided into three periods of two utive days within a period of four weeks. Twen -hour urine specimens were collected in each and on two other occasions The mean values ake of energy, fat, protein carbohydrates, min- nd electrolytes did not differ between the two despite the large differences in BP and obesi- mean values for urinary excretion of miner ectrolytes and nitrogen (calculated as crude n) did not differ between the groups The pres- dings for the effect of salt on BP do not justify tion of the salt intake as a means for decreas- in the population

ords duplicate portion technique energy intake e of minerals and electrolytes high and low blood re levels population study salt intake women

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ty and overweight are important risk factors pertension (6 13 23) and there is evidence decrease in body weight usually leads to a ed blood pressure (BP) (12 29) Therefore reduction should be of value in the treatment pertension However it is common experience weight reduction is difficult not only in the rely obese but even in the large number of ts who are moderately overweight Another risk factor is excessive salt intake (8 21 31) Accordingly a reduced consumption of salt may promote decreased BP (27) and moderate salt restriction has been used either as the sole treatment of mild hypertension (26) or in combination with diuretics (28) Owing to the results of these studies reduced salt consumption as a dietary goal has won official approval in the USA (20)

The present investigation deals with the question whether subjects with high and low BP differ in their dietary habits especially with respect to their intake of energy and salt The investigation was carried out with the duplicate portion technique (3 4)

SUBJECTS

The subjects were selected from participants in an ophthalmological survey performed in the Dalby population during 1969–70 In that study BP was measured in a strictly standardized fashion as described previously (34) The survey comprised 963 females of whom 790 (82%) completed the study All the latter were without antihypertensive treatment at the time of selection From this female population those with BP above the 95th percentile (group A N=36) in the age range 30–79 years were selected and age matched with 36 females selected from those with BP below the 30th percentile (group B) The subjects in group A were selected on the basis of systolic and diastolic BP and pulse pressure they were included if any of these indices or any combination thereof exceeded the 95th percentile in the whole material for the five age groups 30–39 40–49 50–59 60–69 and 70–79 years Subjects were assigned to group B if both the systolic and the diastolic BP were below the 30th percentile The pulse

Abbreviations T_3 = triiodothyronine T = thyroxine BP = blood pressure

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pressure was not used as a select on cri erion for group B n order to avoid including females n whom low pulse pressure was combined w th elevated dia tolic BP

In group A one subject refused to partic pate while another failed to attend all invest gations A th rd was on antihypertens ve treatment and a fourth had developed diabetes mell tus after the first examinat n These four subjects and the r mat hed controls n group B were excluded Furthermore one female from each group failed to manage food sampl ng by the dupl cate port on techr que Hence these two subjects and their matched contrcls were also excluded and each group finally comprised 0 females In 19 5 the age in group A was 5? ± 13 and in group B 5? ± 14 years (mean S D)

METHODS

Anthr pometric and BP measu ements

He ght and we ght were measured accordir, to the WHO recommendat ons (30) Relat ve body we ght was cal u lated as we ght (kg)/he ght (cm) 100 and the ndex of obes ty as we ght (kg)/he ght² (m) (36)

The techn que for BP measurement has been described n detail (33)

B ochemical anables

The analyses of B-hematocrit fB-glucose fS-cholesterol fS-triglycerides and S-urate levels were performed by conventional techniques The analyses of S-triiodothyronine (T_3) and S-thyroxine (T_4) were carried out by select ve radioimmunoassays (5 25)

Sampl ng of food and urine

The dietary hab ts were invest gated during Jan May 1975 The duplicate portion technique (3 4) was used to study the ntake of energy fat prote n carbohydrates and minerals Part c pants were informed about the n estigation and the duplicate portion technique and given prec se instru tions for urine collections The food sampling was carried out w thin a period of four weeks It compr sed six days [illegible] ised into three periods of two concutive days Monday Tuesday Wednesday Thursday and Saturday Sunday During the second day in each of the three periods 24-hour urine specimens were collected (referred to as 19 5 The partic pants also made up written pro ocols—giving not only the type of food eaten but also crude est ma es of the quantities expressed in colloquial terms—for each of the sampl g days in order to trace the source of unexpected values

Anal ses f nu rient and ene gy ntake

The d plicate portions were kept in the refrigerator over n ght and then brought to the laboratory After we ghing the portion was homogenized lyophilized and fat-extracted w th chloroform as described earl er 3 4 In the present study however sodium desoxycholate as emulsifier was changed to Triton® X 100 isooctyl-phenoxy polyethoxy-ethanol Kebo-Gra e Sweden in order to avoid sodium contamination Total fat content was obtained after evaporation of the [illegible] oroform extract The prote n con ent was determ ned as [illegible] ly mod fied Kjeldahl me hod [illegible] gave the crude protein ntake The [illegible] was obtained by [illegible] g fat fre [illegible] prote n and 7 [illegible] ash The ene gy [illegible] from g fat × 9 3 plus protein 4 1 [illegible] by d fference × 4 1 (3 4

M nerals (cal um magnes m [illegible] analysed by atomic absorption [illegible] wet ash ng from the fat f ee ly [illegible] (4) Sodium and potass um we e determ [illegible] photometry as described earlier (4 [illegible] minerals and electrolytes in the urine [illegible] formed in order to compare the dietary intake [illegible] excretion of these subs ances

Furthermo e the 24-hour ur nary excr [illegible] and potass um (19?5 ?) were c [illegible] sponding results from two other 24 [illegible] tions in the two grou s (19? and 19? [illegible] 24-hour urinary excretion of [illegible] 197? and compared w h [illegible] 1975 ?

Sta s cal me h ds

Mean values standard de ia ions coeffici [illegible] t on and correlat on c efficien s were [illegible] ventional methods Most calc [illegible] the Compu er Cen re Uni e sity [illegible] cal analyses were also made with an [illegible] 101 Stat stical s gnificance was [illegible] Student s t test on paired or un [illegible] the ur nary collections was [illegible] variance for sodium and potas um excretion [illegible] occasions (one 197? one 1975 I and [illegible] s gnificance levels are expressed as [illegible] <0 05 ** 0 001 p<0 01 p 0 001 [illegible] symbo s are u ed N=number M [illegible] standard de ia ion DF=degree of freedom [illegible] stat tically s gnificant (p>0 05 [illegible] ficent All values are g en as M SD [illegible] wise stated

RESULTS

Anthr pometric mea urement s

The results n 197? and 19 5 [illegible] The mean values of we ght relat [illegible] and the index of obes ty were [illegible] in group A than n group B The [illegible] d fference in he ght All these values [illegible] sentially unchan d between 19?? and [illegible]

Blood pressu e

The BPs in groups A and B at the [illegible] the follow up exam [illegible] The d fferences n sys [illegible] the two groups pers sted fr m the [illegible] in 1969– 0 to the f llow up exam [illegible] and 19?5 In 19?? mean sy [illegible] BP [illegible]

L Anthropometric measurements in 1972
75

	Group A	Group B	p
(cm)	161±6	163±6	n s
(kg)	76 1±15 7	59 7±10 0	* *
weight	1 24±0 27	0 96±0 17	***
obesity	18 4+4 0	13 9±2 6	***
cm	160±6	162±6	n s
(kg)	76 0+16 1	60 5+9 8	***
body weight	1 25±0 28	0 97±0 17	***
obesity	18 6±4 1	14 1±2 6	***

...itial recordings in both groups ($p<0.01$) In ...stolic BP had decreased ($p<0.01$) Group A ...urned to the initial level while in group B the ...mained higher ($p<0.01$) Diastolic BP varied ...tween the different occasions It was some ...wer in group A in 1975 than in 1969–70 ...5) and higher in group B in 1972 than in 1969– ...0 01) (Table II)

...mical variables

...ematocrit fS triglyceride S T_4 and S urate ...were significantly higher in group A than in ...3 There was no difference between the two ...in fB glucose fS cholesterol or S T_3 levels ...sults in 1975 are given in Table III The ...ces between the groups were similar in 1972 ...75 although the absolute levels were not ...al

...of energy fat protein carbohydrates ...ls and electrolytes

...take of energy yielding nutrients—fat pro...d carbohydrates—is given in Table IV both

II Blood pressures (mmHg) at the first study ...the follow up examinations

	Group A	Group B
BP		
0	175±34	114± 8
	190±34**	130±15***
	179±32	123±19**
ic BP		
70	102±13	73+6
	103±14	76+7**
	97±13*	73+7

...05 * $p<0.01$ *** $p<0.001$

Table III Biochemical measurements in 1975 for the two groups

	Group A	Group B	p
fS Cholesterol (mmol/l)	5 9±1 1	5 5±1 0	n s
fB Glucose (mmol/l)	4 8±0 4	4 6±0 5	n s
B Hematocrit (%)	39±2	37±3	**
fS Triglycerides (mmol/l)	1 10±0 67	0 77±0 59	*
S Urate (μmol/l)	257±51	228±56	*
S T_3 (ng/ml)	1 79±0 27	1 72±0 20	n s
S T_4 (ng/ml)	93±19	84±12	*

in absolute amounts and in per cent of total energy The mean values of energy and energy yielding nutrients in groups A and B did not differ between the six sampling days and no significant differences between the groups were found for any of the studied sources of energy (Table IV) Both groups showed an average daily intake of energy around 6 3–6 4 MJ In group A 35% of the energy originated from fat and 38% in group B Protein constituted 13–14% of the energy in both groups and carbohydrates around 50%

Neither did the intakes of minerals (calcium magnesium zinc copper) and electrolytes (sodium potassium) differ between the groups (Table IV) The sodium intake in both groups amounted to around 100 mmol daily corresponding to an intake of salt of about 6 g/day

Urinary excretion of minerals electrolytes and nitrogen

The mean values for urinary excretion of minerals (calcium magnesium zinc copper) electrolytes (sodium potassium) and nitrogen (protein) showed

Table IV Energy intake during six sampling days

	Group A	Group B
Energy intake		
MJ	6 4±1 5	6 3+1 5
kcal	1525±349	1512+353
Fat (g)	58±16 (35%)	62±18 (38 %)
Protein (g)	52±15 (14%)	48±11 (13%)
Carbohydrates (g)	189+42 (51%)	180±45 (49%)
Sodium (mmol)	105±31	94+25
Potassium (mmol)	55±14	52±12
Calcium (mg)	577+287	577±224
Magnesium (mg)	270+85	243±66
Zinc (mg)	8 1±2 7	8 1±2 9
Copper (mg)	1 50+0 68	1 45+0 49

Table V *Urinary excretion of minerals and protein (nitrogen ×6.25) in studies performed in 1972 and on two occasions in 1975*

	Group A	Group B
1972		
Sodium (mmol)	133±43	120±38
Potassium (mmol)	67±24	56±18
Protein (g)		56±17
1975 1		
Sodium (mmol)	146±54	125±54
Potassium (mmol)	60±19	59±19
1975 2		
Sodium (mmol)	120±32	118±28
Potassium (mmol)	59±12	59±14
Calcium (mg)	146±56	130±61
Magnesium (mg)	67±21	59±25
Zinc (mg)	0 35±0 13	0 27±0 11
Copper (mg)	0 05±0 016	0 05±0 013
Protein (g)	58±13	55±12

no differences between groups A and B (Table V) The values for sodium and potassium were virtually unchanged in both groups between 1972 and the two examinations in 1975 (Table V) Analysis of variance did not show any significant differences between the separate measurements of 24-hour urinary excretions of sodium and potassium in groups A and B respectively (Group A F ranged between 1 41 and 2 40 DF=(4 154) group B F ranged between 0 17 and 0 30 DF=(4 161)) The mean urinary excretion of protein in group B in 1975 2 did not differ significantly from the value in 1972 (Table V) The mean values of sodium potassium and protein in the food were lower ($p<0\ 001$) than the corresponding values for urinary excretion The mean values of urinary excretion of calcium magnesium zinc and copper were lower ($p<0\ 001$) than the consumption

Correlations between some of the investigated parameters

The index of obesity was correlated to mean arterial BP in group A (p 0 001) but not in group B (Table VI) The index of obesity showed negative correlations with the intake of fat protein and carbohydrates in group A ($p<0\ 01$) while corresponding correlations in group B were not significant (Table VI) Dietary protein sodium and potassium were correlated to the corresponding urinary excretion values in groups A and B (p 0 001 or $p<0\ 01$) (Table VI) The intakes of [illegible] showed negative correlations [illegible] in group A ($p<0\ 001$ and p 0 01 [illegible] while the corresponding correlations [illegible] were not significant (Table VI)

DISCUSSION

Epidemiological investigations [illegible] body weight or other expressions [illegible] play a strong association with hypertension [illegible] the present study the index of obesity [illegible] significantly ($p<0\ 001$) to mean arterial BP [illegible] A (high BP) but not in group B (low BP) [illegible] underlined that group A was [illegible] females with the highest BP values [illegible] not on treatment for hypertension [illegible] do not represent a group with established [illegible] sion But they may represent females [illegible] line phase of primary hypertension [illegible] of parameters associated with [illegible] hypertension ought to be of greatest [illegible]

The index of obesity was higher [illegible] group A than in group B and [illegible] mean difference in body weight of [illegible] the groups The higher index of obesity [illegible] could not be explained by any [illegible] energy intake or the intake of separate [illegible] ing components like fat protein or carbohydrates [illegible] fact there were significant negative [illegible] ($p<0\ 01$) between the index of obesity [illegible]

Table VI *Correlation coefficients be[illegible] the investigated parameters*

	Group A	[illegible]
Index of obesity mean arterial BP	0 65 *	[illegible]
Index of obesity intake of fat	−0 4[illegible]	[illegible]
Index of obesity intake of protein	−0 [illegible] *	[illegible]
Index of obesity intake of carbohydrates	−0 [illegible]	[illegible]
Intake of protein urinary excretion of protein	0 [illegible]	[illegible]
Intake of sodium urinary excretion of sodium	0 [illegible]	[illegible]
Intake of potassium urinary excretion of potassium	0 [illegible]	[illegible]
Intake of sodium mean arterial BP	−0 [illegible] **	[illegible]
Intake of potassium mean arterial BP	−0 [illegible] **	[illegible]

$p<0\ 01$ * p 0 001

fat, protein and carbohydrate in group A
in group B
difference in body weight between the
may have to be traced far back in time
the index of obesity was unchanged in both
when examined in 1972 and 1975 The die
tits were studied in 1975 The present finding
obese and normal weight women consumed
amounts of energy is also in accordance with
reports (9) Keen et al (16) in a recent study
ent intake in relation to adiposity and dia
also found a highly significant inverse correla
tween food energy intake and adiposity in
ormal British populations It was suggested
ir findings that higher degrees of adiposity
ociated with food energy intakes lower than
t and hence lower total energy expenditures
er these cross sectional data do not exclude
sibility of a relationship between develop-
of overweight and a concomitant progression
wards higher values

etiology of obesity is however a field for
tion One aspect discussed is the regulation
metabolic rate by thyroid hormones This
e remembered when a decrease in body
is used as a *tool in the treatment of high BP*
oreover and the consumption of energy may
etween those with a high and those with a
ndex of obesity It is of interest in this con
at the S-T_4 level was significantly higher in
than in group B (Table III)

another nutrient suggested to be associated
ypertension was consumed in the same
about 6 g in both groups There was no
ion between salt intake and mean arterial
hich is in accordance with previous findings
group in elderly with a similar mean daily salt
(4-6 g) using the duplicate portion sampling
ue (4) The urinary excretion of salt was
reproducible as demonstrated by analysis of
e The excretions of sodium and potassium
of the same magnitude in the two groups and
ed to the intake but exceeded this by about
($p<0.001$)

ly Bing et al (2) described 24-hour uri
xcretion of sodium as a means of monitoring
intake in patients with essential hyperten
The relevance of this report for the present
lies in the value for urinary excretion which
mmol/24 hours For age and sex matched
s the corresponding value was 152 mmol/24
hours The finding that hypertensive patients and normotensive subjects do not differ in the 24 hour urinary excretion of sodium is also consistent with other studies (7 14 22 32) However conflicting results have been reported on the relationship be tween BP and urinary sodium excretion (1 15 35) Thus Berglund et al (1) found that up to a resting diastolic BP of 90 mmHg sodium excretion rose in agreement with the theory of pressure diuresis (11) Above 90 mmHg however sodium excretion fell with increasing BP It was suggested that the data indicated a curvilinear relationship between BP and salt intake We actually found a very strong nega tive correlation between intake of sodium and BP in the group with high BP This may be interpreted as an expression of such a curvilinear relationship even if the narrow BP distribution in the low BP group may have masked a correlation between BP and salt intake

Before drawing further conclusions from this dietary investigation the validity of the duplicate portion sampling technique has to be discussed The validity may be evaluated by comparing the intake with the output of sodium potassium and nitrogen Their magnitudes ought to be the same if the subject is in metabolic balance and the intake and excretion have been monitored under satisfac tory conditions which are not yet clearly estab-lished Sodium potassium and nitrogen were ex creted in amounts exceeding the intake suggesting an underestimation of the food intake There is also a technical explanation to consider The same chemical methods of analysis were applied to very different raw materials e g urine and mixed lyophilized and fat extracted food homogenate powder In fact losses of about 10% of sodium and potassium have been found during treatment of the food materials (4) Another possibility is unsatisfac tory conditions e g duration choice of days and number of days etc for comparison of intake and excretion

All current methods for measuring dietary intakes have shortcomings in reflecting a true picture of the food intake but when two groups are compared these factors presumably affect both groups equal ly Therefore it seem justifiable to conclude from the present data that dietary factors could not be implicated as a primary cause of discrepancies in BP or body weight between the two groups This conclusion does not rule out the possibility that a diet therapy which reduces the body weight of an

obese patient with hypertension would not be successful It must be mentioned that Parijs et al (28) observed a slight decrease in BP when the intake of salt was halved in patients with hypertension

Roughly speaking both urinary and dietary measurements showed that the salt intake of these women with low and high BP respectively did not exceed 10 g/day Salt restriction has been employed efficiently as evidenced by the rice fruit diet of Kempner which contained approximately 200–500 mg of sodium per day (17) When salt restriction is used to reduce BP the critical level for sodium intake seems to be very low—about 2–3 g/day as shown by hemodynamic investigations (10 19) Therefore the dietary goals outlined for the US (20) with a recommended daily salt intake of about 8 g seem doubtful The present data regarding salt intake do not support restriction of salt intake as a tool for decreasing BP

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REFERENCES

1 Berglund G Wallentin I Wikstrand J & Wilhelmsen L Sodium excretion and sympathetic activity in relation to severity of hypertensive disease Lancet 1 324 1976
2 Bing R F Thurston H & Swales J D Salt intake and diuretic treatment of hypertension Lancet 2 121 1979
3 Borgstrom B Nordén Å Åkesson B & Jagerstad M A study of food Scand J Soc Med (Suppl) 10 1975
4 Borgstrom B Nordén Å Åkesson B Abdulla M & Jagerstad M Nutrition and old age Scand J Gastroenterol (Suppl) 52 1979
5 Burger A Sakoloff C Staeheli V Vallotton M B & Ingbar S H Radioimmunoassays of 3,5,3 triiodo-L thyronine with and without a prior extraction step. Acta Endocrinol (Kbh) 80 58 1975
6 Chiang B N Perlman L V & Epstein F H Overweight and hypertension A review Circulation 39 403 1969
7 Dawber T R Kannel W B Kagan A Donabedian R K McNamara P M & Pearson G Environmental factors in hypertension In The epidemiology of hypertension Proceedings of an international symposium (ed J Stamler R Stamler and T N Pullman) p 255 Grune & Stratton New York 1967
8 Freis E D Salt volume and [illegible] tension Circulation [illegible]
9 Garrow J S Energy balance and [illegible] pp 84–85 North Holland Publishing Co [illegible] 1974
10 Guyton A C Coleman T G [illegible] Manning Jr R D Norman Jr R [illegible] J D A systems analysis approach [illegible] long range arterial blood pressure [illegible] tension Circ Res 35 159 1974
11 Guyton A C Young D B DeClue J [illegible] son J D McCaa R E Cowley [illegible] N C & Hall J E In Pathophysiology [illegible] ment of arterial hypertension (ed [illegible] Hansson and L Werkö) p [illegible] Mölndal 1975
12 Heyden S Tyroler H A Hames C G [illegible] A Thompson J W Krishan I & [illegible] Diet treatment of obese hypertensives [illegible] Med 45 209 1973
13 Hsu P H Methewson F A L & [illegible] Blood pressure and body mass index [illegible] longitudinal study J Chronic Dis [illegible]
14 Karlberg B E & Tolagen K Relation between blood pressure [illegible] plasma [illegible] electrolyte excretion in normotensive [illegible] J Clin Lab Invest 37 521 1977
15 Karvonen M J & Punsar S Sodium [illegible] blood pressure of west and east [illegible] Scand 202 501 1977
16 Keen H Thomas B J Jarrett R J [illegible] J H Nutrient intake adiposity and [illegible] Med J 1 655 1979
17 Kempner W Treatment of hypert[illegible] disease with rice diet Am J Med 4 545 [illegible]
18 Koch F C & McMeekin T L [illegible] nesslerization micro-Kjeldahl method [illegible] tion of the nesslerfolin reagent [illegible] Chem Soc 46 2066 1924
19 Ledingham J M Distribution of [illegible] potassium in heart and skeletal muscle [illegible] mental renal hypertension in rats [illegible] 1953
20 McGovern G Eating in America Dietary [illegible] the United States Report of the Senate [illegible] on Nutrition and Human Needs pp [illegible] 1977
21 Meneely G R & Battarbee H D [illegible] low potassium environment and [illegible] Cardiol 38 768 1976
22 Miall W E Follow up study of arterial [illegible] the population of a Welsh mining [illegible] 2 1205 1959
23 Miall W E Bell R A & [illegible] between change in blood pressure and [illegible] Prev Soc Med 22 73 1968
24 Minari O & Zilversmit D B [illegible] stabilization of [illegible] dabil d acids Anal Biochem 6 [illegible]
25 Miyama T [illegible] Hollander C Serum [illegible] ments in human serum by [illegible]

...ination by gas liquid chromatography J Clin ... 679 1971

... T Gillies A Morgan G Adam W ... M & Carney S Hypertension treated by ... restriction Lancet I 727 1978

... R. J F Effect of rice diet on plasma ... and extracellular fluid space in hypertensive ... J Clin Invest 29 912 1950

... J Joossens J V Van der Linden L Ver... G & Amery A K P C Moderate sodium ...ction and diuretics in the treatment of hyperten... Am Heart J 85 72 1973

... E Abel R Modan M Silverberg D S ... H E & Modan B Effect of weight loss ... salt restriction on the reduction of blood ... in overweight hypertensive patients N Engl ... 298 1 1978

... G A & Blackburn H W Cardiovascular ... methods WHO Monogr Ser 56 93 1968

31 Sasaki N The relationship of salt intake to hypertension in the Japanese Geriatrics 19 735 1964

32 Simpson F O Waal Manning H J Bolli P Phelan E L & Spears G F S Relationship of blood pressure to sodium excretion in a population survey Clin Sci Mol Med 55 373s 1978

33 Thulin T Andersson G & Scherstén B Measurement of blood pressure—a routine test in need of standardization Postgrad Med J 51 390 1975

34 Thulin T Bengtsson B & Scherstén B Assessment of casual blood pressure variations Postgrad Med J 54 10 1978

35 Waern U Findings at a health survey of 60-year old men and recorded diseases during their preceding 10 years of life Thesis Uppsala 1977

36 Zilva J F & Nicholson J P An obesity index and the significance of bromide space measurements Clin Sci 19 449 1960

Table I *Laboratory data on the patients*

Case no	Sex	Age (y)	S T_4 (nmol/l)	Free T_4 index	S T_3 (nmol/l)	TSH (mU/l) Before thyroxine	After thyroxine
Group 2							
1	♀	41	177	203	3 8		
2	♀	42	190	218	5 6		
3	♀	27	216	237	6 6		
4	♀	68	200	202	5 6		
5	♀	36	191	207	2 4		
Group 3							
1	♀	65	8			47	-
2	♀	49	12			40	3 4
3	♀	52	9			46	3 2
4	♂	49	7			49	3 3
Normal values			60–170	45–160	1 4–3 2	<7 2	

SUBJECTS AND METHODS

Group 1 (control subjects infused with verapamil) Five healthy non-obese volunteers 4 women and 1 man 26–56 years of age (mean ± S E M 36±6 years) without family history of hypercalcemia or diabetes

Group 2 (thyrotoxic patients infused with verapamil) Five non-obese women with thyrotoxicosis but without family history of diabetes or hypercalcemia 27–68 years of age (43±7) The diagnosis was based on (*a*) symptoms and signs typical of the disease and (*b*) laboratory tests outlined in Table I At the time of the first investigation none of the patients was on any medication After antithyroid treatment symptoms and signs characterizing the disease disappeared gradually and all patients became euthyroid At that time 4 of them were reinvestigated

Group 3 (hypothyroid patients infused with verapamil) Four patients with primary hypothyroidism 3 women and 1 man 49–65 years of age (54±4) without family history of diabetes or hypercalcemia Features on which the diagnosis was based were (*a*) symptoms and signs [illegible]pical of the disease and (*b*) laboratory data given in [illegible]le I When first investigated none of these patients [illegible] on any medication After oral thyroxine treatment [illegible]mptoms and signs characterizing the disease disappeared gradually in all Three patients were reinvestigated when euthyroid

The participating subjects were informed about the purpose of the study and gave their free consent

Analytic procedures Blood glucose was determined enzymatically with a commercial glucose oxidase preparation (Kabi Reagents Stockholm Sweden) Immunoreactive insulin in serum was assayed by a two-antibody procedure essentially as described by Soeldner and Slone (24) Serum calcium was measured by a flame photometric method

Experimental design All experiments were performed in the morning after an overnight fast and after an equilibration period of approximately 30 min Blood samples for glucose insulin and calcium determinations were drawn from an antecubital vein Verapamil [illegible] via the antecubital vein of the opposite side

Group 1 Basal values for glucose [illegible] were obtained at −10 and −2 min At 0 min [illegible] infusion (Isoptin® Knoll Ludwigshafen am Rhein Germany) was started and kept going at [illegible] 180 min Verapamil 15 mg dissolved in [illegible] was infused in each experiment Blood [illegible] glucose and insulin were drawn every 30 min [illegible] verapamil infusion

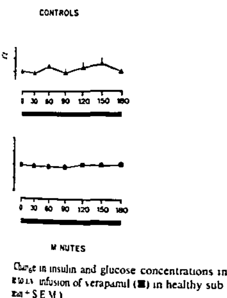
Group 2 All thyrotoxic patients were [illegible] with verapamil as described above for group 1 [illegible] months of oral antithyroid treatment 4 of them were [illegible]vestigated according to an identical experimental protocol At that time all of them were euthyroid

Group 3 The 4 patients with primary hypothyroidism were initially infused with verapamil in exactly the same way as patients in group 1 When [illegible] months of oral thyroxine substitution 3 [illegible] reinfused with an identical amount of verapamil [illegible] period of 180 min

Calculations When evaluating the effect of [illegible] the peripheral blood glucose concentration [illegible] calculations were made In each individual [illegible] ue constituting the mean of 2 preinfusion values [illegible] determined Then the individual glucose [illegible] verapamil infusion were calculated [illegible] tigated whether these glucose changes [illegible] points of time during the verapamil infusion [illegible] nificantly from the control level [illegible] dent's *t* test was applied on paired [illegible] The [illegible] of verapamil on the peripheral venous insulin [illegible] tion was tested in a similar way

RESULTS

Group 1 In this group the mean ± S E M [illegible] glucose concentration was 4 2 ± 0 4 mmol [illegible]



Change in insulin and glucose concentrations in ... to i.v. infusion of verapamil (■) in healthy sub... ...n + S E M)

...ponding concentration of insulin was 6 2±0 6 ...and of calcium 2 3±0 06 mmol/l Verapamil ...affect the peripheral venous glucose or insu... ...centrations as shown in Fig 1

...p 2 The untreated thyrotoxic patients had a ...control glucose concentration of 4 7±0 4 ... Control insulin and calcium concentrations ... ±1 9 mU/l and 2 3±0 04 mmol/l respec... When verapamil was infused glucose started ...fine and reached a level significantly below ...trol value from 60 min on (Fig 2 left) Insu... ...centration however remained unaffected by ...fusion When 4 of the 5 patients in this group were reinvestigated at a time when their thyroid function had normalized their control glucose insulin and calcium concentrations were 4 2±0 3 mmol/l 12 0±0 8 mU/l and 2 3±0 04 mmol/l respectively Verapamil did not affect significantly either the glucose or the insulin concentration at this occasion (Fig 2 right)

Group 3 The control glucose concentration in the hypothyroid group was 4 8±0 3 mmol/l before any medication was instituted The corresponding insulin and calcium concentrations were 6 1±0 4 mU/l and 2 4±0 07 mmol/l respectively Although the blood glucose concentration dropped slightly toward the end of the verapamil infusion this fall was not statistically significant (Fig 3 left) In contrast the verapamil infusion elicited a transient insulin increase (Fig 3 left) Thirty min after the start of the infusion the peripheral venous insulin concentration had increased by 93±14% ($p<0.01$) Thereafter it dropped rapidly and did not differ significantly from the control level from 60 min on When 3 of the 4 hypothyroid patients were reinvestigated after thyroxine substitution their mean basal concentration of glucose was 4 7±0 1 mmol/l of insulin 8 0±3 2 mU/l and of calcium 2 4±0 07 mmol/l This time however verapamil did not affect either the glucose or the insulin concentration (Fig 3 right)

DISCUSSION

In the current as well as in a previous investigation (21) verapamil infused into healthy subjects was

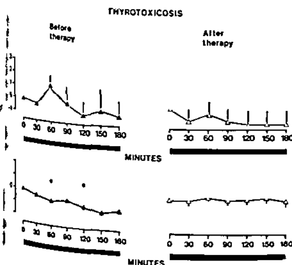


Fig 2 Change in insulin and glucose concentrations in response to i v infusion of verapamil (■) in thyrotoxic patients before and after antithyroid treatment (mean ± S E M) *$p<0.05$ ** $p<0.01$

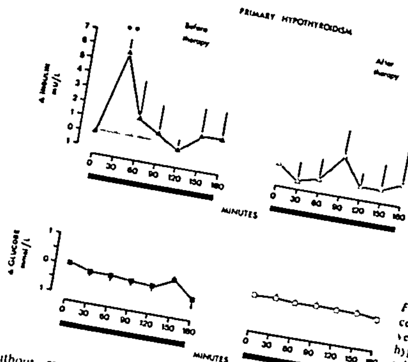


Fig. 3. Change in insulin and glucose concentrations in response to i.v. verapamil (■) in patients with hypothyroidism before and after substitution (mean ± SEM). ** p<0.01

without effect on both insulin and glucose concentrations (Fig. 1). In thyrotoxic patients verapamil brought about a significant fall in glucose concentration whereas insulin concentration remained unaffected (Fig. 2 left). Since verapamil thus induced a decline in glucose in the face of an unchanged insulin concentration, it is reasonable to assume that verapamil might have influenced other glucose regulatory factors than insulin. Glucagon is such a factor. In dogs and in rats the pancreatic secretion of glucagon is inhibited by verapamil (10, 14). If this is also the case in thyrotoxic but not in healthy subjects, the discrepancy between the glucose responses to verapamil infusion in thyrotoxic and healthy individuals seems logical. Although the basal α-cell secretion has been shown to be normal in thyrotoxic patients (22, 23), it is not known whether pancreatic α-cells react normally in thyrotoxic subjects when exposed to a calcium blocking agent. As long as this has not been convincingly shown, the above mentioned hypothesis can neither be supported nor rejected.

Other factors involved in the glucose metabolism which may be affected by verapamil in thyrotoxic patients are catecholamines. It has been maintained that the thyroid hormones potentiate the metabolic effects of catecholamines (13). Adrenal catecholamines accelerate the release of non-esterified fatty acid (NEFA) from adipose tissue (4).

An increased plasma concentration of NEFA has been found in patients with thyrotoxicosis [illegible] 25). Thyrotoxic patients also have an [illegible] take of glucose, thought to be related [illegible] creased availability for oxidation of NEFA [illegible] so it cannot be excluded that verapamil [illegible] ing the secretion of adrenal catecholamines [illegible] the turnover rate of NEFA and thereby [illegible] about an increased peripheral glucose uptake [illegible] ies recently carried out in vitro [illegible] blockade of acetylcholine evoked release of catecholamines by D-600, a calcium [illegible] rapamil derivative (19), support [illegible] Whatever mechanism there may be [illegible] the verapamil induced fall in glucose in [illegible] patients, it is interesting to note that [illegible] abolished by oral antithyroid treatment [illegible] ing the thyroid function (Fig. [illegible])

Hypothyroid patients [illegible] of verapamil in a diffe[illegible] tients (Fig. 3, left) [illegible] lowed by a slight d[illegible] never reached [illegible] level. If cha[illegible] concentrati[illegible] changes in [illegible] suggest th[illegible] insulin fro[illegible] has to be [illegible]

pancreas has to traverse the liver before the periphery A verapamil induced de ... the fractional hepatic retention of insulin be excluded in the hypothyroid patients ... the insulin peak in the peripheral venous these patients might have been due to a de ... hepatic retention of insulin rather than to an ... β-cell secretion Although the current ... tion does not provide evidence either to ... or reject this possibility it shows that ... substitution abolishes the insulin peak and unaffected insulin and glucose concentra ... response to verapamil infusion in hypo... patients (Fig 3 right)

...nclusion the present investigation has ... abnormal and different insulin–glucose ... pattern to verapamil infusion in hyper... thyroid patients which can be restored to ... by medical treatment This may have clini... ...ficance since hyperthyroid patients often ... arrhythmias and angina pectoris and thus ... subjected to verapamil treatment

REFERENCES

... J D & Bondy P K Hypercalcemia of ...toxicosis Ann Intern Med 65 429 1966

... D L Bennett L L & Grodsky G M ...rement for calcium ion in insulin secretion by ...erfused rat pancreas Am J Physiol 214 174 ...

... G Somers G Van Obberghen E & Malais... J Calcium antagonists and islet function I ...tion of insulin release by verapamil Diabetes ...7 1975

... F A Hormonal control of human adipose ... metabolism in vitro In Adipose tissue (ed R ...e & E F Pfeiffer) pp 167–71 Thieme Verlag ...gart 1970

...ky G M & Bennett L L Cation require... for insulin secretion in the isolated perfused ...eas Diabetes 15 910 1966

... C N & Hyams D E Plasma concentrations ...cose non-esterified fatty acid and insulin dur... ...al glucose tolerance tests in thyrotoxicosis ... 69 1964

... C N & Milner R D G Cations and the ...ion of insulin from rabbit pancreas in vitro J ...ol 199 177 1968

...n, W R Laszlo J Bogdonoff M D & Estes ... Alterations in free fatty acid metabolism in ...rine disorders Part I Effect of thyroid hor... J Clin Endocrinol Metab 23 33 1963

...an, B The significance of calcium for glucose ...lation of insulin release Endocrinology 97 392 ...

10 Hermansen K & Iversen J Effect of verapamil on pancreatic glucagon release from the isolated perfused canine pancreas Scand J Clin Lab Invest 37 139 1977

11 Iversen J & Hermansen K Calcium glucose and glucagon release Diabetologia 13 297 1977

12 Kim H Kalkhoff R K Costrini N V Cerletty J M & Jacobson M Plasma insulin disturbances in primary hyperparathyroidism J Clin Invest 50 2596 1971

13 Landsberg L Catecholamines and hyperthyroidism In Clinics in endocrinology and metabolism (ed L Landsberg) pp 697–718 Saunders London 1977

14 Leclercq Meyer V Marchand J & Malaisse W J The role of calcium in glucagon release Studies with verapamil Diabetes 27 996 1978

15 Levy J Herchuelz A Senrer A & Malaisse W J Inhibition by verapamil of calcium influx in the β-cell Diabetes (Suppl) 2 400 1975

16 Lundqvist I Fanska R & Grodsky G M Interaction of calcium and glucose on glucagon secretion Endocrinology 99 1304 1976

17 Milner R D G & Hales C N The role of calcium and magnesium in insulin secretion from rabbit pancreas studied in vitro Diabetologia 3 47 1967

18 Ortigosa J L Mendoza F Argote R M Garcia G Cervantes C & Parra A Propranolol effect on plasma glucose free fatty acid insulin and growth hormone in Graves disease Metabolism 25 1201 1976

19 Pinto J E B The blocking effect of magnesium on the secretion of adrenal catecholamines induced by the omission of sodium from the extracellular medium Horm Metab Res 11 404 1979

20 Rojdmark, S Counter regulation of basal insulin secretion during alcohol hypoglycemia in hypercalcemic and normocalcemic man Acta Med Scand 201 45 1977

21 — Effect of verapamil on insulin response to alcohol hypoglycemia in patients with primary hyperparathyroidism Diabetes 28 20 1979

22 Seino Y Goto Y Taminato T Ikeda M & Imura H Plasma insulin and glucagon responses to arginine in patients with thyroid dysfunction J Clin Endocrinol Metab 38 1136 1974

23 Shima K Sawazaki N Tanaka R Morishita S Tarui S & Nishikawa M The pancreatic alpha and beta cell responses to l arginine and insulin induced hypoglycemia in hyperthyroidism Acta Endocrinol 83 114 1976

24 Soeldner J S & Slone D Critical variables in the radioimmunoassay of serum insulin using the double antibody technic Diabetes 14 771 1965

25 Wajchenberg B L Cesar F P Leme C E Souza I T Pieroni R R & Mattar E Carbohydrate metabolism in thyrotoxicosis Studies on insulin secretion before and after remission from the hyper thyroid state Horm Metab Res 10 294 1978

26 Yasuda K Hurukawa Y Okuyama M Kikuchi M & Yoshinaga K Glucose tolerance and insulin secretion in patients with parathyroid disorders N Engl J Med 292 501 1975

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Renal Function and Morphology in Long-Term Lithium and Combined Lithium-Neuroleptic Treatment

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ACT Ten patients on long term lithium and ten on lithium and neuroleptics (com therapy) were examined with renal biopsy of renal function Patients on combination had more pronounced histopathological and lower concentrating capacity than pa lithium alone Patients on combination had received a larger total dose of lithium had higher maximum serum lithium levels tients on lithium alone Patients with large volumes had a low concentrating capaci re was a negative correlation between degree pathological lesions and urinary concentrat acity Estimation of urinary concentrating seems to be of value for the assessment of sions in lithium treatment

lithium neuroleptic therapy urinary concen apacity antidiuretic hormone kidney pathology ed Scand 208 381 1980

been known for many years that lithium can renal lesions in animals (9) Lithium intox is also known to be a serious condition in and renal lesions following lithium intoxica have been reported (7) Reports on the renal athology in man have been few (6 8) The of Hestbech et al (8) on chronic renal lesions a focal fibrosis and nephron atrophy in pa who had been on lithium treatment for several prompted us to perform a study on the renal on in patients on long term lithium treatment le found that most patients had an impaired concentrating capacity even after withdrawal lium (5) We also found that patients who were d with both neuroleptic drugs and lithium had concentrating capacity than patients treated lithium alone (2)

aim of the present study was to examine the morphology in lithium treatment and compare it with the results of renal function tests We also wanted to know if patients treated with both lithium and neuroleptic drugs have a renal morphology which differs from that of patients treated with lithium alone

PATIENTS

Twenty patients on long term lithium treatment were studied They were divided into two groups one consisting of five males and five females aged 52 8±10 0 years who had been treated with lithium alone (lithium group) and the other of four males and six females aged 39 6±10 2 years who had received both lithium and neuroleptic drugs (combination group) The latter patients had been treated with so-called major tranquilizers (haloperidol chlorpromazine fluphenazine perphenazine and others) in different combinations and doses for more than one year Patients receiving only small doses of neuroleptics e g for sleep disturbances were not included Data concerning the lithium treatment are given in Table I

The patients had no known disorders except mental illness or side effects of drug therapy Nine patients in the lithium group had discontinued their lithium intake two months before the examination In the combination group three patients had stopped taking lithium one patient had had lithium intoxication two years before the examination and one had previously unknown hypothyroidism without clinical signs at examination One patient in each group received thyroxine therapy for hypothyroidism

METHODS

All patients were examined at the Unit of Nephrology Department of Internal Medicine Umeå University From the patient journals we calculated how many months the patients had received lithium therapy and the total dose of lithium consumed (Table I) We also extracted from the journals all previous determinations of serum lithium concentration which had been performed every third month or more often in blood samples taken 12 hours after the last intake of lithium The highest single value was noted (Table I) The blood pressure was recorded at presentation Urinary protein and glucose were determined qualitatively Urinary sediment was examined with phase contrast microscopy (10) The daily urine volume serum

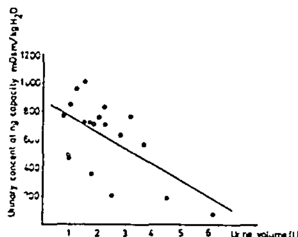


Fig 3 Relation between urinary concentrating capacity (DDAVP test) and daily urine volume (r=0 61) Symbols as in Fig 1

(3/10) The three patients in group C were all receiving combination therapy There was a negative correlation between daily urine volume and concentrating capacity (Fig 3)

DISCUSSION

The patients in this study were selected from a larger patient population on long term lithium therapy They were not randomly selected so this study cannot answer the question about the frequency of renal lesions in patients on long term lithium therapy Patients on combination treatment had more pronounced lesions in the biopsies than patients treated with lithium alone The difference was however not statistically significant which might be due to the rather crude method of grading the lesions found in the biopsies The lesions as previously reported (4) seem to be of a nature similar to that described by Hestbech et al (8) One explanation of the less severe renal lesions found by us than by Hestbech et al might be that most of their patients had had lithium intoxication The reason for our finding of more severe histopathological changes in the combination group than in the lithium group is obscure Neuroleptic drugs per se or in combination with lithium may be harmful to the kidney The higher maximum serum lithium concentration in the combination group might also be the critical factor In our opinion a high peak serum lithium level is a more likely reason for the differences between the groups than the larger total dose of lithium or the longer duration of treatment in the combination group [illegible] supported by the finding that [illegible] with the most pronounced lesions [illegible] peak serum lithium level but they [illegible] very large total doses of lithium [illegible] longer than the others (Table II) [illegible] results do not permit us to [illegible] which factor is the most important [illegible] of serum lithium or neuroleptic [illegible] the patients on combination therapy [illegible] maximum serum lithium levels [illegible] lithium alone? The explanation [illegible] several patients on combination therapy [illegible] severely psychotic and had not been [illegible] their lithium therapy adequately [illegible] psychosis

The renal function correlated [illegible] the biopsy findings All patients [illegible] lesions had a urinary concentrating [illegible] than 400 mOsm/kg patients [illegible] sions (group C Table II) had lower [illegible] capacity Determination of urinary [illegible] capacity might be of value [illegible] with renal lesions who might be at [illegible] ing more severe renal disease if [illegible] continues The indication for [illegible] treatment should be very strong [illegible] very low urinary concentrating [illegible] therapy cannot be withdrawn [illegible] ly controlled with frequent measure[illegible] hour lithium concentration in serum [illegible] of daily urine volume might lead to [illegible] clusions as measurement of [illegible] capacity

ACKNOWLEDGEMENTS

This work was supported by grants from [illegible] Minnesfond [illegible] Stiftelsen [illegible] the Medical Faculty of the University [illegible]

REFERENCES

1 Asplund K [illegible] test in assessment of renal function [illegible] therapy Lancet [illegible]
2 Bucht G & Wahlin A [illegible] trating capacity [illegible] Lancet [illegible]
3 — Renal [illegible] treatment and after [illegible] Scand 20 [illegible]

a. G Wah n A Wentzel T & W nblad B
ρkador d behandl ng med l t um och neurolep-
Nord Psykiatr T dsskr 32 445 1978

a. G Wahlin A & W nblad B Renal concen
ng cap c y in pa ents w th long term l th um
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a meeting about l th um treatment and k dney
ase, arranged by the b olog cal sect on of the
nd Ps h a nc Assoc at on Copenhagen Oct
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s. G D Da es B & K nca d Sm th P
e tubular les ons after l th um Lancet 1 1310

7 Chapman A J & Lew s G lat ac e l l po son ng A case report w l nec p y l l s J Okla State Med Ass c 65 591 1972

8 Hestbech J Hansen H E An d en A et l Ch on c renal les ons following long te t t c w th l th um Kidney Int 12 15 1977

9 Radomsk J L Fuyat H N Nel n A A et l The tox c effects excret on and d st b t n f l l t chlor de J Pharm Exp Ther 100 429 1950

10 Wahl n A D fferent al count f u y k l cytes mononuclear leukocytes and ren l e l cl l cells Umeå Univers ty Med cal D sse t ns New ser es no 42 Umeå Sweden 1978

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PRELIMINARY REPORT

Hypoglycemia in Alzheimer's Disease

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ACT Glucose tolerance tests (GTT) were [illegible]ed on patients with *a*) dementia of Alzheimer [illegible] distal gangrene, *c*) cerebrovascular disease, [illegible] non-diabetic controls Fasting blood sugar [illegible]ficantly lower and the areas under the GTT were significantly smaller in the dementia [illegible] in the other three groups It is discussed [illegible] Alzheimer's disease is a generalized disease [illegible] confined to brain tissue and whether the [illegible] blood glucose levels could impair the brain [illegible] levels

[illegible] Alzheimer's disease glucose metabolism
[illegible] Scand 208 387 1980

[illegible] of the most common dementia de[illegible] of Alzheimer type is still unknown The [illegible] of the brain in this disease is well de[illegible] and reports on abnormalities in both [illegible]aminergic and cholinergic systems have [illegible]blished However it is not known whether [illegible] these defects have any effect on the [illegible] systems in the body Carbohydrate [illegible] is dependent at least in part on the [illegible] hormones and the catecholaminergic and [illegible] transmitter systems exert an influence [illegible] hormones Furthermore it has been shown [illegible] impairment of glucose oxidation by reduc[illegible] of the glucose concentration produces a de[illegible] synthesis of acetylcholine (1) Accordingly [illegible] subnormal blood glucose levels in pa[illegible] with dementia of Alzheimer type could be due [illegible] in the transmitter systems It could also [illegible] explanation of the finding of reduced [illegible] synthesis in this disease After in vit[illegible] of brain biopsy material it was consid[illegible] that a generalized defect in glucose [illegible] would cause the diminished acetyl[illegible] production (4)

PATIENTS AND METHODS

Four groups of patients were investigated Group 1 [illegible] patients (mean age 70 y) who fulfilled the criteria of dementia of Alzheimer type (insidious onset loss of memory intellectual and personality deterioration typical non-fluctuating progressive downhill course absence of hypertension stroke or other diseases causing dementia) group 2 247 patients (mean age [illegible] y) with distal gangrene group 3 62 patients (mean age [illegible] y) with cerebrovascular disease group 4 [illegible] unselected non-diabetic control patients (mean age [illegible] y) most of whom where hospitalized because of deep venous thrombosis or heart failure

Oral glucose tolerance tests were performed according to a standardized procedure and the areas under the glucose tolerance test curves were calculated as described earlier (2)

RESULTS AND DISCUSSION

After excluding all cases with open diabetes we found significantly lower fasting blood sugar determined by the glucose oxidation method in group 1 (4 34 mmol/l) than in all other groups controls ($p<0\ 02$) group 2 ($p<0\ 005$) and group 3 ($p<0\ 005$) The numerical values of the areas under the glucose tolerance test curves (2) were also significantly smaller in the dementia group than in the other three groups (Fig 1)

The investigation suggests that patients with dementia of Alzheimer type have a changed carbohydrate metabolism with decreased blood glucose levels In order to check whether these results are due to an underlying malabsorption or not we have undertaken a preliminary study on 9 patients with dementia of Alzheimer type and found normal values in their xylose absorption tests Seven out of 9 patients had normal results in the vitamin A ab-

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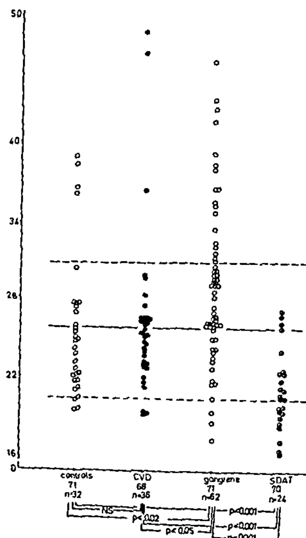


Fig 1 Oral glucose tolerance test *CVD* = cerebrovascular disease *SDAT* = dementia of Alzheimer type

sorption test the two exceptions having a slightly diminished vitamin A absorption From these results it would appear that malabsorption is unlikely

It seems more likely that the changed carbohydrate metabolism is due to malfunction in the hormonal regulation for example in the brain pituitary adrenal axis in which the cholinergic and dopaminergic transmitter systems play an important role Dementia of Alzheimer type has been suggested to be a generalized disease not confined to the brain tissue (5) Catecholamines somewhere else in the body e g in the liver make it difficult to mobilize the carbohydrate stores An interesting question is to what extent at all dementia of Alzheimer type and diabetes mellitus in old age coexist It has been suggested that for the peripheral nervous system a slight decrease in glucose levels leads to exhaustion of the neuronal firing It remains to be found out whether or not the decreased glucose levels can impair the acetylcholine synthesis as extensively as found by independent groups in the brain of patients with dementia of Alzheimer type

ACKNOWLEDGEMENTS

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REFERENCES

1 Gibson G E & Blass J P Impaired acetylcholine in brain accompanying hypoglycemia and mild hypoxia J Neurochem 27 37 1976
2 Lithner F Cutaneous erythema with or without necrosis localized to the legs and feet—a lesion in elderly diabetics Acta Med Scand 196 333 1974
3 Perri V Sacchi O & Casella L Nervous transmission in the superior cervical ganglion of the deficient rat Q J Exp Physiol 55 25 1970
4 Sims N R Smith C C T Davison A N D M Flack R H A & Snowden J S metabolism and acetylcholine synthesis in neuronal activity in Alzheimer s disease Lancet 1980
5 Winblad B Adolfsson R Gottfries C G L & Roos B E Brain monoamines metabolites and enzymes in physiological and senile dementia. Recent Dev Mass Spectrom Med 1 253 1978

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Effect of Different Kinds of Fibre on Postprandial Blood Glucose in Insulin Dependent Diabetics

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RACT D etary fibre may retard glucose ab- n in normal and d abetic subjects It is how nclear wh ch type of fibre would be most for this purpose We therefore studied er pectin differs from fibre from barley (85%) rus (15%) (Dumovital®) in its effect on post al blood glucose responses Eight insulin de nt diabet cs fasted overnight and were then a meal w thout their morning insulin The basic composed of 90 g wh te bread and 120 g jam carbohydrate 105 g) was given three times w h 15 g pect n and with 15 g Dumovital Blood glucose was measured for three hours sts howed that pectin administration consider hib ed the postprandial rise in blood glucose Dumo tal showed no such effect Barley/citrus a mixture of cellulose hemicellulose lign n pectin) has not the same inh b ting effect on randial rise in blood glucose as pure pectin in n-dependent diabet cs Thus the specific type of must be cons dered when prescrib ng dietary to diabet cs

ord d etary f bre pect n bran nsul n-dependent s b ood gluco e

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pr pal aim n the treatment of d abetes mel s to no mal ze the blood glucose Even with al an d abet c agents and nsul n the diet s a stone n the treatment In recent decades a) of d e ary regimes have been used but to he d abe c pat ent s adv sed to eat a normal th some rest ct ons (1) Surpris ngly l ttle s n, howe er about how d fferent foodstuffs x u es of foods affect the postprand al rise n glucose One of the food components wh ch tracted ncreased attent on s d etary f bre l ns et al (5) showed that add t on of pect n uar gum (both potent gell ng agents) to a test meal d m n shed the postprandial rise in blood glu cose and nsulin n non nsul n dependent d abet cs The same was shown in insul n dependent d abet cs and healthy volunteers (3 6) Guar gum and pect n g ven alone have the same effects When 7 d abet cs (6 on insul n 1 on d et alone) were g ven 25 g guar gum da ly in add t on to the r usual d et for one week periods the r mean urinary glucose excret on decreased 40–50% (7) The insul n dose was not reduced during the study Other stud es where d ets rich n fibre (mixture of cellulose hem cel lulose l gn n and pectin) have been g ven to d abet ics for a longer period (2 weeks 15 months) have resulted n mproved d abetes control (2 9 10)

The above ment oned stud es nd cate that some types of d etary f bres are able to mprove d abetes control most l kely by nh b t ng the absorpt on rate of monosacchar des n the upper gastro ntest nal tract The effect of pect n and guar gum seems obvious but what about other types of commerc al f bre m xtures? This was our departure for compar ing the effect of pect n and barley bran on the post prand al r se n blood glucose n nsul n dependent d abet cs

PATIENTS AND METHODS

The study s based on experimen s w h e ght nsul n de pendent d abet cs who were rece v ng nsul n tw ce daily Table I conta ns relevant pa ent data Each pa en was g en three d ffe ent test meals (Table II) a bas c break fast alone and the same breakfast e her w th 15 g pect n added to one component (the jam) or w th 15 g Dumov tal® f b e (Dumex) Dumov tal s a commerc al f bre m xture w dely used as a d etary supplement n Norway It s a m xtu e of cellulose hem cellulose l gn n and pect n composed of 85% barley bran and 15% c trus f b e

The test meals were g ven after an overn gh fast The

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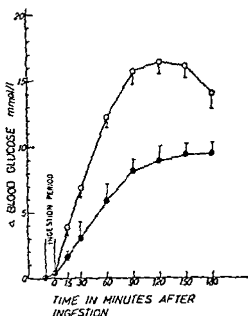


Fig 1 Average postprandial increase in blood glucose after the basic meal (O) and after the basic meal supplemented with 15 g pectin (●)

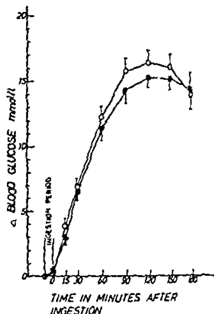


Fig 2 Average postprandial increase in b after the basic meal (O) and after the supplemented with 15 g barley bran (●)

subjects had taken their afternoon dose of insulin on the day before but did not take their ordinary morning insulin before the tests Meals were consumed in 10 min Capillary blood samples were taken in the fasting state and at 0 15 30 60 90 120 150 and 180 min following the meal Blood glucose was determined enzymatically with glucose oxidase (Glox)

Statistics Wilcoxon test for pair differences

RESULTS

Figs 1 and 2 show the average increase in blood glucose (± S E M) after each of the three meals Addition of 15 g pectin to the basic meal gave a marked reduction in the postprandial rise in blood glucose The difference is statistically significant ter 15 ($p<0.005$) 30 ($p<0.025$) 60 ($p<0.01$) 90 120 150 ($p<0.005$) and 180 ($p<0.025$) r... reduction was found after addition of 15 g bran

DISCUSSION

Our finding that addition of pectin to a te diminishes the postprandial rise in blood gl insulin dependent diabetics is in good acc with findings by others (3 5 6) Addition of bran had no such effect in our patients Th can be compared with a study by Jenkins e who found that 42 g wheat bran (12 g dietar added to an oral glucose tolerance test in 6 volunteers had no significant effect on th

Table I *Data on the patients*

	Mean	Range
Age (y)	23	17–31
Duration of diabetes (y)	6	3–11
Insulin requirement (IU)		
Morning		
NPH insulin	31	24–48
Rapid acting	12	2–44
Afternoon		
NPH insulin	22	12–48
Rapid acting	6	4–10

Table II *Composition of the test meals*

Foodstuff	Weight (g)	Carbohydrate (g)	En (kJ
1 Basic meal			10
White bread	90	48	9
Strawberry jam	120	56	0
Total	210	104	
2 Basic meal + 15 g pectin (suspended in the jam)			
3 Basic meal + 15 g Dumovital® fibre (suspende jam)			

rise in blood glucose and insulin In that mouth-caecum transit time was measured ent types of fibre Pectin delayed the tran by 15 min guar gum by 75 min while bran d it by 45 min These differences were ed on the basis of differences in viscosity seems to be positively correlated to the in effect on the postprandial rise in blood

ence from studies on breath hydrogen (6) e excretion patterns of xylose (8) and tamol (4) ind cates that the effect of pectin ar gum is due to slower absorption of car ates rather than malabsorption Pectin and gel-forming agents could elicit various effects gastro ntestinal tract I Slower gastric empty prolonged intest nal transit time (4) II of carbohydrates in a gel or viscous solu ould retard the diffusion of digestive prod towards the absorptive mucosal surface III cation of gastrointestinal hormone responses IV Interference with glucose absorption the intestinal membrane Dumovital fibre ture of cellulose hemicellulose l gnin and did not seem to have any effect on the ption of carbohydrates in our short term But as previously mentioned fibre mixtures to have effects on diabetes regulation in long stud es (2 9 10) These studies are how more difficult to interpret because in making fibre diet, other components (e g the amount arbohydrate protein and fat) have been ed. Even though we could have short and term effects of fibre mixtures on carbohydrate bolism Possible mecanisms for this could be ight degree of malabsorption II Modification strointestinal hormone responses III Influ on the transport across the absorptive mem es

is report clearly shows that different types of ry fibre can have different effects on the absorption of nutrients from the gastrointestinal tract the specific type of fibre must be considered prescribing d etary fibre to diabetics

REFERENCES

1 American Diabetes Association Princ ples of nutrition and d etary recommendat ons for nd viduals with diabetes mellitus 1979 Diabetes 28 1027 1979

2 Anderson J W & Ward K Long term effects of h gh-carbohydrate h gh-fiber d ets on glucose and l pid metabolism A prel m nary report on patients w th diabetes Diabetes Care 1 77 1978

3 Goulder T J Alberti K G M M & Jenkins D J A Effect of added f ber on the glucose and metabolic response to a mixed meal in normal and d abetic subjects Diabetes Care 1 351 1978

4 Holt S Heading R C Carter D C Prescott L F & Toth H P Effect of gel f bre on gastric emptying and absorption of glucose and paracetamol Lancet 1 636 1979

5 Jenkins D J A Goff D V Leeds A R Alberti K G M M Wolever T M S Gassull M A & Hockaday T D R Unabsorbable carbohydrates and diabetes Decreased postprandial hyperglycaemia. Lancet 2 172 1976

6 Jenkins D J A Leeds A R Gassull M A Cochet B & Alberti K G M M Decrease in post prandial insulin and glucose concentrations by guar and pectin Ann Intern Med 86 20 1977

7 Jenkins D J A Wolever T M S Hockaday T D R Leeds A R. Howarth R Bacon S Apling E C & D lawari J Treatment of diabetes w th guar gum Lancet 2 779 1977

8 Jenkins D J A Wolever T M S Leeds A R Gassull M A Haisman P Dilawari J Goff D V Metz. G L & Alberti K G M M D etary f bres f bre analogues and glucose tolerance Importance of viscos ty Br Med J 1 1392 1978

9 Kiehm T G Anderson J W & Ward K Beneficial effects of a h gh carbohydrate h gh f ber d et on hyperglycemic d abetic men Am J Clin Nutr 29 895 1976

10 Miranda, P M Horw tz D L H gh f ber d ets in the treatment of diabetes mell tus Ann Intern Med 88 482 1978

11 Morgan L M Goulder T J Tsiolakis D Marks V & Alberti K G M M The effect of unabsorbable carbohydrates on gut hormones Diabetologia 17 85 1979

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Circulating Protein Complexes in D-Penicillamine Therapy of Rheumatoid Arthritis

Co relat o i bet ee i IgG a id α_1 A ititry psin IgA Co nplexes a id Cl i ca l Resp ise

Renee Norberg Frank A Wollheim and Per O Gedda

D pa ment of I nolog tl e Na onal Bacter olog cal Laborator y Stockl ol n D s o i of Rl e atolog Depart nent of Med c ne Un ers ty of Lund Mal o General Hosp tal Maln o and tl e Department of Rl e matology Central County Hosp al Orebro S eden

ACT Eighteen of 24 patients with rheu arthritis showed intermediate IgG con complexes on preparative ultracentrifugation treatment with D penicillamine Serial s of these showed strikingly close correlation uct on of IgG as well as α_1 antitrypsin IgA xes. Three patients did not respond to treat inically and reta ned both types of complexes xes virtually disappeared in all responders small changes were found in total IgG or IgM and the reduction of IgA levels was moderate for one case who developed IgA deficiency portance of further analysis of non responders ssed

ords pen c llam ne treatment rheumato d arthrit s prote n complexes th ol act v ty

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el as be ng a metal chelator D pen c llam ne A) has a strong aff n ty for th ol groups in vivo ng m xed d sulph des with extracellular th ol pounds l ke cyste ne and ome plasma prote ns Normal human plasma conta ns S–S linked exes between α antitryps n and IgA wh ch be cleaved on m ld reduct on in vitro (8) The of the α antitrypsin IgA complexes decrease dly n rheumato d arthr tis (RA) pat ents re ng to D-PA treatment (15)

ulat ng IgG complexes considered to conta n G RF are frequently demonstrated n pa th RA (10 13) Also these complexes de after D-PA therapy (11)

s paper is an extension of these observations the aim to study the behav our of both com s multaneously in the course of D PA treat in RA

MATERIAL AND METHODS

Cl n cal ater al

The effect of D PA treatment on c rculat ng IgG com plexes was stud ed in RA pat ents at the Department of Rheumatology County Hosp tal Örebro

Sera were drawn from all pat ents before therapy and then at control v s ts at irregular nter als All sera were kept at -20°C unt l analys s Sera from 24 out of 66 pa t ents were subjected to grad ent centr fugat on analys s Before D-PA treatment sera from 17 of these 24 pat ents conta ned c rculat ng IgG complexes mostly of nter med ate size These sera and subsequent sera from the same pat ents were analyzed for the presence of α anti tryps n IgA complexes and IgG complexes Moreover the serum values of IgG and IgA and IgM were determ ned as well as t tres of rheumato d factor (RF)

All pat ents from whom sera were taken fulf lled the American Rheumat sm Assoc at on criteria for def n te or class cal RA The n tial D PA dose was 250 mg/day and was ncreased monthly to 750 mg n a few pat ents to 1000 mg

Grad ent centr f gat on analys s

Th s was performed n a Sp nco SW 50 rotor as described earl er (10) The fractions obta ned after grad ent cen trifugat on were subm tted to rad al mmunodiffus on as say for IgG If IgG was detected n fract ons correspond ng to sed mentat on coeff c ents >9S th s ndicated p es ence of IgG complexes

Deter na on f IgM IgG a d IgA

Immunoglobul ns were determ ned by s ngle rad al m munod ffus on (9)

α Ant tryps n IgA con plexes

These were demonstrated by the crossed immunoelec trophores s techn que (2) The complex concentrat on was est mated from the area under the precip tation arch in the β zone when us ng rabb t anti-α ant tryps n n the gel of second d mens on run (8 15)

Abb e a ons D-PA=D-pen c llam ne RA rheumato d arthrit s RF=rheumato d factor

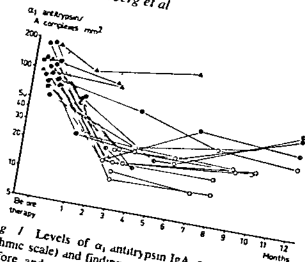


Fig 1 Levels of α_1 antitrypsin IgA complexes (logarithmic scale) and findings of IgG complexes in RA sera before and at various intervals during D-PA therapy ○ = No demonstrable IgG complexes ◐ = IgG complexes at borderline level ● = finding of IgG demonstrable IgG complexes These patients did not respond clinically to D-PA ▲ = The lines connect values from the same patients

Determination of α_1-antitrypsin in serum

This was performed by the electroimmunoassay according to Laurell (7)

Determination of rheumatoid factor in serum

The Latex fixation test with human gammaglobulin was performed with reagents from Hyland Laboratories Los Angeles California

RESULTS

Figs 1 and 2 show determinations of α_1 antitrypsin IgA complexes and the findings of IgG complexes in sera from 17 RA patients before and at various intervals during (Fig 1) and after D-PA therapy (Fig 2) The pretreatment levels of α_1 antitrypsin IgA complexes were within the expected normal ranges As can be seen from Fig 1 the values decreased after D-PA therapy and remained at low levels during treatment The behaviour of the IgG complexes paralleled closely that of the α_1 antitrypsin IgA complexes In samples taken 3 months after initiation of therapy IgG complexes could be demonstrated only in single sera In 8 patients D-PA had to be withdrawn depending on various side-effects In all sera taken 1–12 months after therapy the α_1 antitrypsin IgA complexes had reappeared and reached approximately the initial levels IgG complexes were demonstrated in all but one sample (Fig 2)

Three patients did not respond to D-PA IgG complexes were demonstrated in all samples d… ing treatment and the levels of α_1 antitryp… plexes were higher than in the responders (…

As can be seen from Fig 3 the IgG IgA values decreased slightly during treatme… ferences between values before and 4 mo… D PA therapy were statistically significa… 0 01) tested by χ^2 test In one patient with noglobulin values within the normal range… D-PA therapy the initial IgA value 1 8 … creased to 0 45 g/l after one month of t… After three months it was 0 1 g/l and rema… that level after withdrawal of more than D PA therapy The RF titres decreased m… more than IgM values (Fig 4)

DISCUSSION

The capability of sulph hydryl reagents to dissociate 19S RF and macroglobulins prompted Jaffe to try D-PA treatment in RA was however soon realized that direct disso… of RF was not a likely mode of action for D… RA (5) A decrease in IgM RF titre that can be demonstrated in most cases is obviously not … by dissociation of the IgM molecule The … usually more pronounced in IgM RF than … whole IgM serum pool Moreover the lo… IgM RF titres usually persist for months after … sation of D-PA treatment which is diffic… concile with a direct reducing effect on the IG… molecule Pritchard and Nuki (12) presen… ly a hypothesis postulating a normalizing … of D-PA on pathologic structures of IgG in RA

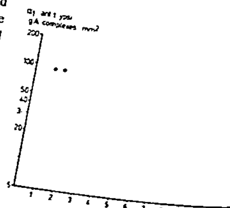


Fig 2 Levels of α_1 antitrypsin-IgA complexes and findings of IgG complexes in RA sera at various intervals after D-PA therapy Symbols as in Fig 1

lead to less RF formation The production of IgM RF but only small ...tal IgM may be interpreted to support ... which however needs further direct ... proof

...haracterized by a strong tendency to ... disulphides in vivo It is excreted in the ... in the form of D-PA cysteine disul... y explanation of the disappearance of ... n IgA complexes would be the block ... ree penultimate SH group on newly ... IgA (15) This would lead to a slow fall ... treatment and a slow increase after ... g D-PA administration The IgG com... ed to be immune complexes contain... are not known to involve intermolecu... bonds The behaviour however of ... s of complexes in the D PA treated ... RA was strikingly similar as is their ... reducing agents in vitro This may ... milar mode of action of D-PA on both ... n and Ig complexes It is of special ... the complex persistence previously ... on responders (14 15) was again con...

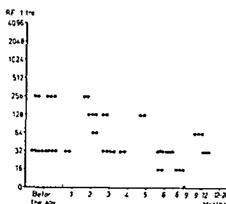


Fig 4 Latex titres in RA sera before and during D-PA therapy

firmed in this series We have evidence that non responders did absorb and metabolize D PA The reduction in their plasma cystine levels and urinary excretion of D PA cysteine mixed disulphide did not differ from that of the responders (14 15) One must therefore look for other explanations of their unresponsiveness

Laurell (personal communication) obtained recently unexpected findings when administering radiolabeled α_1 antitrypsin complexed with likewise labeled cysteine kappa chains and IgA respectively The disappearance rates of the complex components were more or less identical with those of the free components This strongly indicated that the complexes are in rapid exchange rather than long lived The SH blocking theory for D-PA action is not supported by these experiments

Altered redox equilibrium leading to a relative depletion of cysteine and a reduced intracellular redox potential may be the relevant biochemical action of D-PA in RA Rapid elimination of D PA and its metabolites (4) calls for explanation of the rather gradual return of the protein complexes after withdrawal of D PA It is conceivable although speculative that D-PA may give rise to secondary enzyme induction involving redox regulation which may affect physiologic and pathologic complexes some time after treatment Along the same line non responders might show some aberrant regulation of their redox balance making them resistant to intracellular reduction by D PA Further analyses of primary non responders as well as patients in therapeutic escape would be of great interest



...IgA IgG and α_1 antitrypsin values (log ...) in RA sera before and at various inter... ...A therapy

ACKNOWLEDGEMENTS

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REFERENCES

1 Deutsch H F & Morton J I D ssoc at on of human serum macroglobul ns Sc ence 125 600 1957
2 Ganrot P O Crossed mmunoelectrophores s Scand J Cl n Lab Invest (Suppl) 124 39 1972
3 He mer R & Feder co M Depolymerizat on of the 19S ant bod es and the 22S rheumato d factor Cl n Ch m Acta 25 41 1958
4 Jaffe I A Compar son of the effect of plasma pheres s and pen c llam ne of the levels of c rculat ng rheumato d factor Ann Rheum D s 22 71 1963
5 — The effect of pen c llam ne on the laboratory parameters n rheumato d arthrit s Arthr t s Rheum 8 1064 1965
6 Jellum E & Skrede S B olog cal aspects of th ol d sulph de react ons during treatment w th pen c l lam ne In Pen c llam ne research n rheumato d d s ease (ed E Munthe) pp 68–77 Merck Sharp and Dohme Oslo 1976
7 Laurell C B Electro mmuno assay Scand J Cl n Lab In est (Suppl) 124 21 1972
8 Laurell C B & Thul n E Complexes n human plasma between α ant tryps n and IgA and α ant tryps n and fibrinogen Scand J [illegible] 7 1975
9 Manc n S Carbonara A O & [illegible] Immunochem cal quan ta ion of [illegible] rad al mmunod ffus on Immuno[illegible] 1965
10 Norberg R IgG complexes n ser[illegible] arthrit s pat ents Scand J Immunol [illegible]
11 Norberg R & Gedda P O Effe[illegible] IgG complexes n rheuma o d arthri[illegible] w th pen c llam ne In Penicillam[illegible] rheumato d d sease (ed E Munthe) Merck Sharp and Dohme O lo 1976
12 Pritchard M H & Nuk G G[illegible] A proposed mode of act on n[illegible] based on syno al flu d analys s Ann [illegible] 37 493 1978
13 W nchester R J Kunkel H G & [illegible] Occurrence of gammaglobul n comp[illegible] and jo nt flu d of rheuma o d arth[illegible] Med 134 286s 1971
14 Wollhe m F A Jepps on J O & Laur[illegible] Plasma α ant tryps n IgA complexes pl[illegible] and urinary cyste ne pen llam ne d[illegible] t on In Pen c llam ne research in [illegible] eases (ed E Mun he) pp 15 160 Merck [illegible] and Dohme O lo 1976
15 — D pen c llam ne t eatment n rheumato[illegible] mon ored by plasma α ant tryp n-IgA com[illegible] and plasma and urinary sulphur containing [illegible] ac ds Scand J Rheum (Suppl) 8 1 1979

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Flexible Fiberoptic Bronchoscopy in Sarcoidosis

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Twenty nine patients with clinical X ray and histology consistent with sar ave been studied with flexible fiberoptic y (FFB) and scalene node biopsy The yield from bronchial mucosal biopsies was from transbronchial lung biopsy 43% the patients showed epithelioid cell as with FFB (lung and/or mucosal biopsies) with 79% with scalene node biopsy Three howed extensive bronchial mucosal changes osing processes due to sarcoidosis Sar f the bronchial mucosa is a frequent find- B is the best method for discovering bron osal sarcoidosis with or without stenosing In our opinion, FFB has a place as a ethod in diagnosing sarcoidosis

bronchial mucosal biopsy flexible fiberoptic opy lung biopsy sarcoidosis scalene node

cand 08 397 1980

ethods are available today for obtaining enal from patients with sarcoidosis The ymph node biopsy (2) is a well known procedure with a high diagnostic yield in s (6 12) Biopsies can also be taken oronchial mucosa (3 11 14) and the lung uring flexible fiberoptic bronchoscopy nethod which has been much discussed in rs

n of this study was to compare the diag d from FFB with a well known diagnostic scalene node biopsy and to find out if any place in the routine investigation of ith suspected sarcoidosis

PATIENTS AND METHODS

eight month period (Feb -Sept 1977) we 9 new cases of sarcoidosis seen at our depart e were 14 women and 15 men with a mean age (range 22–70) The age and sex distribution is ig 1 The patients were assigned to one of three stages according to their chest X ray findings stage I (hilar lymphadenopathy) stage II (pulmonary infiltra tion) and stage III (pulmonary fibrosis)

FFB was performed under topical anaesthesia Bron chial mucosal biopsies were taken from three standard places 1) right upper lobe bronchus 2) right middle lobe bronchus 3) left upper lobe bronchus and elsewhere when macroscopical changes in the mucosa were seen Transbronchial lung biopsy (TBL) (1) was taken from the right lower lobe in 14 of the 29 patients TBL was per formed only in patients in stages I and II one to three biopsies were taken from each patient Scalene node biop sy was performed in 28 of the 29 patients

If neither scalene node biopsy nor bronchoscopy gave histological evidence of sarcoidosis other methods such as biopsies from skin muscle and mediastinoscopy were applied for achieving histological evidence of sarcoidosis

RESULTS

Of the 29 patients 13 had a chest X ray consistent with stage I 13 with stage II and 3 with stage III In 28 of the 29 patients studied scalene node biopsy and/or biopsy with FFB revealed non-caseating epithelioid cell granulomas The diagnostic yield from each method is shown in Table I The his tological evidence of sarcoidosis was obtained by mediastinoscopy in one patient Of 28 patients with positive biopsies from scalene node biopsy and/or FFB 9 had positive biopsies with both methods 6 with FFB alone and 13 with scalene node biopsy alone

There was no significant difference in the diag nostic yield from any of the three standard places of bronchial mucosal biopsy (Table II) Biopsies taken from microscopically changed areas however showed much higher frequency of sarcoid infiltra tion TBL was performed in only 14 patients and lung tissue was obtained from all of them The result is shown in Table I

Abbreviations FFB = flexible fiberoptic bronchoscopy TBL = transbronchial lung biopsy

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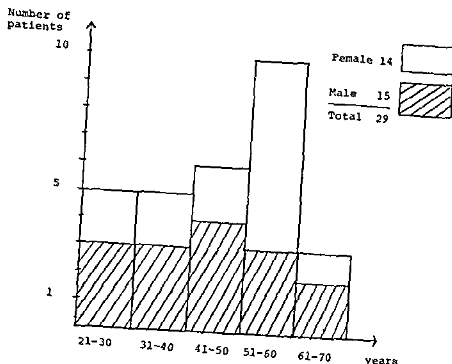


Fig 1 Age an
tion of 29 pa
coidosis

During bronchoscopy we found macroscopical changes in the bronchial mucosa in 15 (50%) of our patients Thickened inflamed bronchial mucosa was found in 13 patients and was the most usual macroscopical change Yellow white plaques were also often seen in the larger bronchi of some patients The mucosal thickening was extensive in three patients leading to almost total bronchial stenosis Two patients had stenosis of the right middle and upper lobe bronchi both with partial atelectasis on the chest X ray Stenosis of the apical segmental bronchus of the left lower lobe was seen in one patient

Table I Diagnostic yield from FFB and scalene node biopsy in 29 patients with sarcoidosis (no of patients with positive biopsies/no of patients biop

Stage	FFB Mucosal biopsy	TBL	TBL and/or mucosal biopsy	Scalene lymph node biopsy
I	4/13	3/6	6/13	9/12
II	6/13	3/8	7/13	10/13
III	2/3	0/0	2/3	3/3
Total				
n	12/29	6/14	15/29	22/28
%	41	43	52	79

DISCUSSION

Non caseating epithelioid cell granulor
tent with sarcoidosis were found in 4
patients with a higher frequency in sta
than in stage I (31%) This result is in
with studies by others (11 14) Ståhle (11
bronchial lesions as fine parallel runn
like a broam mucosal swelling lo
stenosis of the bronchi and flat ye
plaques In our study 50% of the patien
macroscopical changes of the same type
frequency of sarcoid infiltration like in s
others (10 14) was found in biopsies ta
macroscopically changed areas

We found a low diagnostic yield with T
method revealed sarcoid granulomas in o
(six out of 14 patients) The reason for
frequency of positive biopsies with TBL w
ably the low number of biopsies taken f
patient In other studies (4 5) with six-e
sies from each patient the diagnostic yi
TBL is 83–90% The diagnostic yield with T
thus increase by taking multiple biopsies (I

The total diagnostic yield with FFB wh
tissue and mucosal biopsies were taken was
figure much lower than that found by Teirste
(13) The difference is probably due to th
diagnostic yield from TBL in o r We
79% positive scalene

Result of mucosal biopsies from different locations in the bronchial tree (no of positive of biopsies taken)

Bronchial mucosal biopsies

Right upper lobe	Right middle lobe	Left upper lobe	Macroscopical changes elsewhere in the bronchial mucosa
1/13	2/13	0/13	1/4
3/13	4/13	4/13	3/6
1/3	2/3	2/3	0/0
5/29	8/29	6/29	4/10
17	28	21	40

according to the literature (6 7 10 12) paring the diagnostic yield from scalene y and FFB in the present study the od seems preferable Lung tissue or mucosal biopsy were however positive atients in whom Daniel s biopsy failed to ogical diagnosis of sarcoidosis

esting feature in our study was the find nsive changes in the bronchial mucosa in nts leading to a partial bronchostenosis t X ray will in such cases often show and may sometimes arouse suspicions of neoplasm (9) These patients have often e symptoms with cough wheezing and and the prognosis seems rather poor (3) ases early corticosteroid treatment could prevent chronic fibrotic bronchosteno-

s in our opinion in spite of the rather low yield in the present study a place as a ethod in the diagnosis of sarcoidosis copy is a necessary procedure for estab diagnosis of bronchial sarcoidosis espe h bronchial stenosis The combination of ode biopsy and bronchoscopy will in most e histological evidence of non caseating d cell granulomas in patients with sar

REFERENCES

" R Bjornstad Pettersen H Lundgren R vist G Stjernberg N & Thunell M Trans bronchial lung biopsy via the flexible fiberoptic bron choscope Lakartidningen 76 4511 1979

2 Daniels A A method of biopsy useful in diagnosing certain intrathoracic diseases Chest 16 360 1949

3 Honey M & Jepson E Multiple bronchostenosis due to sarcoidosis Br Med J 2 1330 1957

4 Khan A Corona E Masson R & Whitcom M Transbronchial lung biopsy for sarcoidosis N Engl J Med 295 225 1976

5 Koerner K Sakowitz A Appelman R Becker N & Schoenbaum S Transbronchial lung biopsy for the diagnosis of sarcoidosis N Engl J Med 293 268 1975

6 Lillington G A & Jamplis R W Scalene node biopsy Ann Intern Med 59 101 1963

7 Lofgren S & Snellman B Principles and proce dures for obtaining biopsies in sarcoidosis Acta Med Scand (Suppl) 425 225 1964

8 Mitchell D N Scadding J G Heard B E & Hinson K F W Sarcoidosis histopathological de finition and clinical diagnosis J Clin Pathol 30 395 1977

9 Olsson T Bjornstad Pettersen H & Stjernberg N Bronchostenosis due to sarcoidosis A cause of atelectasis and airways obstruction simulating pulmo nary neoplasm and chronic obstructive lung disease Chest 75 663 1979

10 Selroos O The frequency clinical picture and prog nosis of pulmonary sarcoidosis in Finland Acta Med Scand (Suppl) 503 1969

11 Ståhle I Bronchial involvement in pulmonary sar coidosis Acta Med Scand (Suppl) 425 234 1964

12 Stjernberg N Truedsson H & Bjornstad Pettersen H Scalene node biopsy in sarcoidosis Acta Med Scand 207 111 1980

13 Teirstein A Chuang M Miller A & Siltzbach L Flexible bronchoscope biopsy of lung and bronchial wall in intrathoracic sarcoidosis Ann NY Acad Sci 278 522 1976

14 Wiesner B Diagnostic bronchologique de la sar coidose Les Bronches 23 308 1973

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Epidemiological Studies in the Upernavik District, Greenland

Incidence of Some Chronic Diseases 1950–1974

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An epidemiological survey of several ... in the Upernavik district, Northwest ... is reported The study population (ap... inhabitants) is one of the remaining whal... populations in Greenland It was ... the 25 year period 1950–74 as to the ... he diseases, which was based on all cases ... in hospital during this period The disease ... the Greenlanders differs from that of ... an populations, having a higher fre... oplexy and epilepsy but a lower frequen... of acute myocardial infarction, diabetes ... thyrotoxicosis bronchial asthma, multiple ... psoriasis The distribution of cancer ... rs from that of the Danish population but ... incidence of cancer is of the same mag... comparable studies should be per... Greenlandic districts that are character... profound changes in life style, in order ... e the effect of these changes on the disease

... incidence chronic diseases Greeland
... Scand 208 401 1980

...e population of Greenland mainly Es... been living under extreme conditions for ... of years epidemiological studies there ... to elucidate etiological factors of diseases ... (1) showed in a comprehensive study ... pattern of diseases in the population of ... differed considerably from that in Den... applies to chronic as well as acute dis...

...ertelsen s survey the disease pattern in ... has not been investigated systematically ... ch studies would be of special interest in view of the intense industrialization and the changes in standard of living which have taken place in Greenland during the last 20–30 years

We have therefore carried out an epidemiological study with regard to fertility mortality and the incidence of some chronic diseases observed during 25 years in a population of whalers and sealers in Greenland The present report deals with the disease pattern the results concerning fertility and mortality will be presented elsewhere

MATERIALS AND METHODS

Study population

The study covers the Greenlandic population i e persons born in Greenland and/or with Greenlandic mothers in the district of Upernavik in Northwest Greenland demarcated by the Thule district (lat 75 N) and the Umanak district (lat 72° N) In 1950 the district had a population of Greenlandic origin of 1 398 persons and 1 887 persons in 1974 The proportion of persons of other origin (mostly Danish) remained constant at 5–10%

The population living in Upernavik town and ten settlements along the coast is traditionally occupied mainly with whaling and sealing fowling and to a lesser degree fishing This traditional diet can be supplemented by Danish food Apart from periods of construction work (harbours schools etc) the only occupation is whaling and sealing or employment in public services or administration During 1950–74 social development was concentrated to Upernavik town where trade schools telecommunications and public administration underwent considerable development In 1952 30% of the Greenlandic population of the district were living in Upernavik town in 1972 37%

The housing standard in the district as a whole has improved during the last 30 years as the turf huts of earlier times have been replaced by standard wooden houses

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Table I Nu iber of observed person yeers d s trib ted by sex age and observ ti n per ods

Age (y)	Males		Females	
	1950-6?	1963-74	1950-6?	1963-74
0-6	2 ?49	3 1 9	2 096	? 753
7 14	1 686	2 895	1 843	2 611
15-?4	1 719	1 425	1 738	1 387
25-39	1 654	1 907	1 684	1 860
40-64	1 633	1 643	1 643	1 671
≥65	194	392	?84	376
Total	9 135	11 391	9 ?88	10 658

The hosp tal (establ shed in 1950) s located n Uper nav k town and employs two Dan sh doctors nurses trained n Denmark and ass stants tra ned n Greenland The settlement of Kraulshavn n the northern part of the d strict some 150 m les from Upernav k town has a s nall nurs ng stat on Apart from better fac l t es for adm tting patients to other hosp tals primarily n Godthåb—the cap tal of Greenland—the heal h fac lit es have not changed much since 1950

S udy mater al

The study covers the 25 year period 1950-74 and the fol lowing d seases are ncluded cancer (all types) apoplexy ep lepsy (grand mal) pept c ulcer acute myocard al n farct on rheumat c fever chron c polyarthrit s chron c pyelonephrit s chron c glomerulonephrit s d abetes mel l tus psorias s psychos s (man c-depress ve react ve psychos s and sch zophrenia) mult ple scleros s and thyrotox cosis

From the f les of the Upernav k Hosp tal we registered all cases of the abo e ment oned d seases n wh ch the n t al d agnos s had been made during hosp tal zat on n the study period The name date of b rth and date of death when applicable were recorded together w th the exact date of d agnos s

V tal stat st cal data

The d stribut on by sex and age (6 age groups) of the population of Greenland s known from censuses carr ed ut at ary ng intervals as a rule about every f ve years urthermore the numbers of males and females reg s tered b rths dea hs and m grations of the Greenland c population are known for each year Deta led informat on on m grat on s lack ng n the local publ c registry but t s known that n 1950-74 there were 1 540 new arr als and ? ?90 departures from the d strict correspond ng to a erage annual arrival and departure rates of 3 8% and 5 7% respect vely of the popula ion Unfortunately t is not known whether the same indi iduals move back and forth just as the age of the ndiv duals mov ng is unregistered It is also probable that not all m grations are registered

Analyses

On the bas s of the data on age and sex together w th those on the size of the study population we est mated the number of person years b erved in ea sum ng that the person years f r those ng the d strict cancel out For the asses changes n the incidence of the d eases period we d ded th s arb rar ly into and 1963-74 S nce the age s ru ure est mated the standard zed total number d sease during the f rst per od u ng the son years n the age classes for the la standard

RESULTS

The material comprises 149 d agnose ndividuals 8 of whom entered the diagnoses each

To perm t further analyses the da are presented separately n an appe shows the number of person years each age and sex group and obser Table II surveys the cases observed of the study per od can be compared ease by relating the standard zed num 6? with the number observed n thermore we show the expected nu total study period) est mated on European ma nly Danish age spec rates

DISCUSSION

The value of ep dem olog cal stud es w present are based on hosp tal records large measure on the val d ty of the di the completeness of the material This concern n the present case as the stud is w dely scattered w th l m ted pos commun cation in certa n seasons and have only lim ted facil t es for diagr dures However spec al zed ass stan c ta ned e ther from d str ct consultants c ferring the pat ents to Godthab or Denm

The diseases ment oned are mostly eas ly d agnosed even on a purely cl Most likely the results contain underest to the absence of cases wh ch certa nosed or were treated out of ho p tal e g d strict doctor vis ted the settlements order to obtain a homogeneous bas s fo mates that we dec ded to restrict oursel admitted to the only regional hosp tal T tance of the sources of error w l be d ther in relation to each lowing sect ons

The cases distributed by diseases sex and observation periods

-d numbers with the age structure for 1963–74 as the standard are given in parentheses

	1950–62		1963–74		1950–74	Expected no 1950–74	Reference no
	♂	♀	♂	♀	♂ + ♀	(♂ + ♀)	
	4 (5 0)	11 (11 1)	13	18	46	53	3
tract incl							
glands	0 (0 0)	4 (4 2)	4	1	9	1 3	3
	0 (0 0)	0 (0 0)	2	2	4	13 7	3
e tract	3 (4 0)	0 (0 0)	2	4	9	5 1	3
	0 (0 0)	3 (3 1)	0	2	5	5 6	3
tal system	0 (0 0)	3 (2 9)	1	4	7	8 1	3
	1 (1 0)	1 (0 8)	3	1	6	1 5	3
unspecified	0 (0 0)	0 (0 0)	1	4	5	17 1	3
	6 (10 1)	5 (5 5)	8	6	25	15 0	6
(grand mal)	5 (5 9)	5 (7 0)	2	4	16	8 0	9
	4 (4 5)	2 (2 1)	10	3	19	29 0	2
	5 (6 0)	1 (1 1)	2	3	11		
polyarthritis	3 (3 7)	5 (5 4)	0	1	9		
	2 (1 8)	0 (0 0)	3	5	10	8 0	5
lonephritis	0 (0 0)	2 (1 9)	2	0	4		
is	0 (0 0)	1 (1 3)	0	1	2		
yocardial infarction	0 (0 0)	1 (1 0)	1	1	3	40 0	11
	0 (0 0)	1 (1 1)	1	0	2	40 0	10
	1 (1 0)	0 (0 0)	0	0	1	25 0	16
mellitus	0 (0 0)	0 (0 0)	1	0	1	9 0	19
oxicosis	0 (0 0)	0 (0 0)	0	0	0	7 0	12
rosis	0 (0 0)	0 (0 0)	0	0	0	2 0	8

found 46 cases of cancer (17 males and 29 The diagnosis had been confirmed by his- l examination and/or operation in all but a es mostly old patients admitted in the ter aase in whom the diagnosis was based ex ly on clinical findings The incidence doub- the first part of the observation period to ond primarily due to more cases among The increase could be explained by impro- ctics and/or increased frequency of zation This applies especially to the male ion in which cancer is generally appearing ages where diagnosis and attempts at have been stepped up

distribution of the various types of cancer is in Table II together with the expected num on Danish incidence rates (3) The total males and females is somewhat lower We found an excess of parotid and al cancers in males as well as females confirms the findings of recent studies (13 he number of cases of lung and gastrointesti ers was however expected

The low occurrence of lung cancer seems credible as throughout the study period the total population has had annual X ray examinations in connection with the mass tuberculosis campaign (18) Persons suspected of cancer would thus be examined more closely It is remarkable that the four cases of lung cancer occurred in the second part of the study period possibly a consequence of the fact that cigarette smoking became more common during and after the Second World War

Of the seven cases of female genital cancers two were vaginal one cancer of the ovaries—all diagnosed in the beginning of the study period—and four cervix cancers diagnosed in 1972–74 This finding is in accordance with the results of Nielsen et al (15) who described an almost explosive development of cervix cancer in Greenland on account of increasing promiscuity

Apoplexy acute myocardial infarction

The material includes a total of 25 cases of apoplexy equally divided between the first and second parts of the study period The diagnosis was purely clinical in all cases and the result must be consid

ered a minimum as many fatal cases are not in cluded and less serious cases especially those from minor settlements have not been hospitalized It is worth noting the considerable excess of this disease compared to the Danish population—only 15 cases should be expected on the basis of figures from a Danish study (6)

On the other hand acute myocardial infarction is rather rare We found only 3 cases of which two must be considered uncertain due to incomplete data in the hospital records and unspecific ECG changes Based upon experience from a Danish study we had expected about 40 cases (11)

The low incidence of acute myocardial infarction combined with the high incidence of apoplexy might be related to the reduced platelet aggregation ability in Eskimos (4) This might well serve as a protec tion against coronary thrombosis at the same time as it involves a greater bleeding tendency leading to apoplexy on a hemorrhagic basis

Epilepsy

In this group we have included only cases of grand mal epilepsy which did not occur together with other diseases (mongolism cerebral palsy etc) Because it is doubtful whether cases of psychomotor and petit mal epilepsy have been diagnosed in Greenland such types of epilepsy have not been included The diagnosis of grand mal epilepsy is based primarily on information or obser vation of at least two convulsive attacks unrelated to rise of body temperature furthermore a large proportion of the cases were verified by EEG dur ing admissions to Danish hospitals

The number of cases (16 altogether) is twice that expected from Danish conditions (9) which con firms previous results from Greenland (7) Surpris y the incidence during the first part of the ob- vation period was twice that in the second part

Peptic ulcer

The number of cases of this disease is subject to some reservation since the food in Greenland often causes retrosternal pains and ructus Especially at the beginning of the study period when X ray examinations were limited and of poor quality the diagnoses were based on clinical findings only and it might be a matter of chance whether a case was diagnosed as gastritis or peptic ulcer Furthermore it must be assumed that slight attacks of the disease never led to hospitilization In 3 cases during the first and 9 during the second part of the period the diagnosis was verified by one or the following findings Large niche on X ra na hematemesis or the finding of ulcer operation We found 19 cases against pected from Danish experience (?) The d cy could be explained by undiagnosed case a lower frequency of admissions especi beginning of the observation period On hand the increase in the number of cases first to the second part of the period may be real

While the ratio between stomach and ulcer in the above mentioned Danish s 1 5 we found stomach ulcer twice as duodenal ulcer

Other diseases

These diseases are of rare occurren e sults should be treated with reservation.

The pronounced reduction in cases of *thritis chronica* during the study period obvious explanation apart from a possib tion with improved housing conditions It noted that serious cases of this disease admitted to hospital for examination rheuma tests) this being a condition for an invalidity pension Four patients from and one from the second period had typical joint changes rheumatic nodules rheuma tests or effect of gold treatment.

The increase in *psychoses* (only schiz manic-depressive and reactive psychoses is probably misleading as a psychiatric service has existed in Greenland only In addition probably only a limited psychiatric cases are being admitted nosed) in Greenland as a consequen e of problems We found 5 manic-depressive 2 schizophrenias and 3 reactive psychos cases were expected (5) but as the ascerta our material seems somewhat low the dence of psychoses may be higher in Gree

The low occurrence of *bronchial asth* also be emphasized (1 case observed cases expected according to Danish e (16)) The case was a middle aged male not been diagnosed in children

Diabetes mellitus was found in only o who during hospitalization for hyperte adipositas showed increased fasting bl

..abetic glucose tolerance curve The patient ..ated with diet On the basis of a Norwegian (9) 9 hospitalized new diabetes cases should ..ated during the study period of which 5 be of the early insulin dependent type The ..uency of diabetes mellitus in Greenland has ..ly been reported by Sagild et al (17) and perhaps—as far as the insulin-dependent concerned—be related to the low frequency Eskimos of the HLA antigens generally as ..d with this form of diabetes In this con the absence of *thyrotoxicosis* (expected 7 according to a Danish investigation (12)) ..sting as it may be assumed that immuno-reactions play an important role in the etiol ..d pathogenesis of this disease

..asis was found in two persons—both of Danish and Greenlandic origin but not re ..d with fair complexion In a study from the Islands (10) the annual incidence was esti ..o be one new case per 1 000 inhabitants The of cases thus expected in our study popula ..ould be at least 40 as younger people in the disease most often appears from a ..y Even if some cases never figure in hospi there can be no doubt as to the relative ..ency of the disease espeically among Green of preponderant Eskimo origin

..lly it should be emphasized that no cases ..tiple sclerosis were found The expected ..r according to Danish incidence rates (8) be about 2 This disease has never been ..d among Greenlanders

..conclude that the pattern of the diseases in ..l in our study differs from that of Western ..e as we have found frequent occurrence of ..xy and grand mal epilepsy but rare or non ..ence of acute myocardial infarction diabetes ..us thyrotoxicosis bronchial asthma multiple ..sis and psoriasis Furthermore the distribu ..f cancer types is different although the total ..nce of cancer equals that of Western Europe ..ring the study period there was possibly an ..asing incidence of cervix cancer and lung ..r Epilepsy and chronic polyarthritis seem to decreased during the period

..en though urbanization and industrialization ..ss advanced in the few remaining sealing dis ..s of Greenland including our study population ..way of life has in many ..come more ..opean Thus it is remark.. ..eases like acute myocardial infarction and diabetes mellitus have not become more frequent

In spite of the restrictions and reservations on account of the size of the material we present it for its descriptive value and also for purposes of com parison with studies in other districts in Greenland with more profound social changes The study has been designed with special reference to such future investigations

ACKNOWLEDGEMENTS

Financial support was obtained from the Danish Medical Research Council (grant no 512 8623) and the Commis-sion for Scientific Research in Greenland

APPENDIX

Cases of chronic diseases in Upernavik district Green land 1950 to 1974 (age at diagnosis year of diagnosis in parentheses)

Cancer of the upper respiratory tract incl salivary glands Males 60 (68) 47 (71) 68 (72) 44 (74) Females 55 (54) 27 (57) 33 (57) 63 (62) 60 (67) *Cancer of the lungs* Males 48 (63) 62 (64) Females 57 (66) 62 (70) *Cancer of the digestive tract* Males 59 (57) 59 (60) 66 (60) 66 (69) 74 (70) Females 39 (65) 60 (65) 65 (69) 42 (71) *Cancer of the breasts* Males 0 Females 49 (50) 49 (50) 34 (51) 45 (69) 60 (69) *Cancer of the urogenital system* Males 74 (65) Females 45 (50) 15 (59) 37 (62) 25 (72) 35 (72) 47 (73) 21 (74) *Sarcoma* Males 47 (58) 41 (64) 73 (72) 22 (73) Females 27 (57) 0 (64) *Others and unspecified* Males 70 (73) Females 0 (63) 69 (63) 65 (69) 8 (72) *Apoplexy* Males 44 (52) 70 (58) 64 (60) 65 (61) 68 (62) 70 (62) 67 (63) 62 (64) 74 (65) 74 (67) 61 (69) 86 (69) 76 (74) 79 (74) Females 56 (50) 25 (51) 64 (51) 78 (51) 43 (62) 69 (65) 57 (66) 66 (66) 66 (68) 60 (70) 75 (74) *Epilepsy (grand mal)* Males 24 (53) 14 (56) 15 (59) 3 (60) 30 (60) 27 (64) 10 (65) Females 8 (51) 14 (51) 5 (59) 7 (59) 10 (60) 1 (63) 7 (60) 4 (70) 2 (74) *Peptic ulcer* Males 25 (56) 37 (59) 50 (59) 35 (60) 24 (63) 58 (64) 44 (69) 32 (70) 41 (71) 43 (71) 56 (72) 66 (73) 35 (74) 54 (74) Females 32 (56) 49 (59) 32 (69) 39 (69) 50 (71) *Rheumatic fever* Males 33 (51) 10 (54) 31 (54) 17 (55) 29 (60) 33 (64) 12 (70) Females 30 (59) 17 (65) 12 (70) 22 (74) *Chronic polyarthritis* Males 31 (55) 19 (56) 8 (59) Females 30 (50) 26 (53) 13 (54) 49 (58) 17 (59) 24 (64) *Psychosis* Males 20 (51) 50 (59) 41 (69) 49 (70) 44 (71) Females 35 (63) 41 (64) 37 (71) 45 (71) 56 (74) *Chronic glomerulonephritis* Males 30 (68) 11 (69) Females 15 (53) 31 (58) *Chronic pyelonephritis* Males 0 Females 38 (59) 83 (73) *Acute myocardial infarction* Males 31 (73) Females 52 (59) 63 (71) *Psoriasis* Males 7 (74) Females 26 (55) *Bronchial asthma* Males 41 (60) Females 0 *Diabetes mellitus* Males 55 (71) Femal.. *Thyrotoxicosis* Male 0 Females 0 *Multiple scl..* Males 0 Females 0

REFERENCES

1 Bertelsen A Grønlandsk medicinsk statistik og nosografi I–III Meddelelser om Grønland hæfte 117 Copenhagen 1940

2 Bonnevie O En deskriptiv epidemiologisk undersøgelse af ulcussygdommen i Københavns Amt Ugeskr Laeger 137 1313 1975

3 Clemmesen J Statistical studies in the aetiology of malignant neoplasms III Acta Pathol Microbiol Scand (Suppl) 209 1969

4 Dyerberg J Bang H O & Stoffersen E Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis Lancet 2 117 1978

5 Fremming K H Morbid risk of mental diseases and other mental abnormalities in an average Danish population (thesis) Munksgaard Copenhagen 1947

6 Hansen B Steensgaard & Marquardsen J Incidence of stroke in Frederiksberg Denmark Stroke 8 663 1977

7 Harvald B & Hels J Medfødte misdannelser i Grønland En efterundersøgelse af 757 børn født i Godthåb 1957–64 Ugeskr Laeger 132 919 1970

8 Hyllested K Disseminated sclerosis in Denmark Prevalence and geographical distribution (thesis) University of Copenhagen Copenhagen 1956

9 Juul Jensen P & Ipsen J Prævalens og incidens af epilepsi i Stor Åhus Ugeskr Laeger 137 2380 1975

10 Lomholt G Psoriasis prevalence spontaneous course and genetics A census study on the prevalence of skin diseases on the Faroe Islands (thesis) Gad Copenhagen 1963

11 Madsen M & Eriksen L S A[illegible] farkts epidemiologi i Storkøbenhavn [illegible] 141 1152 1979

12 Mogensen E F & Green A The [illegible] thyrotoxicosis in Denmark Incidence [illegible] cal distribution in the Funen Region [illegible] Med Scand 208 183 1980

13 Nielsen N Hojgaard Mikkelsen F & [illegible] J P Nasopharyngeal cancer in Greenland [illegible] dence in an arctic Eskimo population [illegible] Microbiol Scand (A) 85 850 1977

14 — Incidence of salivary gland neoplasms [illegible] with special reference to an anaplastic [illegible] Acta Pathol Microbiol Scand (A) 86 185 [illegible]

15 — Carcinoma of the uterine cervix and [illegible] Greenland Acta Pathol Microbiol Scand [illegible] 1978

16 Petersen E Bach & Hagn-Meincke F E[illegible] og prognose for patienter med kronisk bro[illegible] asthma bronchiale Ugeskr Laeger 140 9[illegible]

17 Sagild U Littauer J Sand Jespersen C & [illegible] sen S Epidemiological studies in Gree[illegible] 1964 I Diabetes mellitus in Eskimos [illegible] Scand 179 29 1966

18 Stein K P S Lange P Krebs Gad [illegible] E Tuberculosis in Greenland Arch En[illegible] 17 501 1968

19 Ustvedt H J & Olsen E Incidence of [illegible] mellitus in Oslo Norway 1956–65 Br J Prev Soc [illegible] 31 251 1977

Acta Med Scand 208 407–410 1980

Aneurysm of the Popliteal Vein as a Cause of Pulmonary Embolism

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Bo Eklof and Knut Wintzell

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ACT A case of recurrent pulmonary em condary to thrombosis in an aneurysm of vein is described The source of em not obvious clinically, and it was dis ly after venography The anomaly was to surgical intervention and the patient was his source of embolism We have found lar case in the literature

pulmonary embolism popliteal vein aneu

Scand 208 407 1980

dence of and mortality from deep venous sis and pulmonary embolism in apparently people is unknown Breckenridge and Rat estimated the minimal incidence of unex aths due to pulmonary embolism in sup normal persons to be at least 2 7 per per year by reviewing the coroner s records of a metropolitan county in Ohio The total incidence of pulmonary embolism disregarding age and underlying disease is also unknown and probably not diagnosed in the majority of cases (3) One can only speculate that pulmonary embolism is underdiagnosed in apparently normal persons

We would like to report a case of pulmonary embolism of unusual origin in a popliteal vein aneurysm in a healthy young man

CASE REPORT

A 37 year-old man previously healthy except for varicose veins of the legs was admitted to the hospital after a syncopal attack at home At arrival he complained of breath-correlated pains in the right upper thorax

Clinical examination revealed a tachycardia of 120/min an acute thrombophlebitis of the distal part of the greater

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Fig 1 Lung scintigram on the day of admission showing perfusion defect in the right upper lobe

a

b

Fig 2 Venogram of the left leg showing venous defects and pr
aneurysm of the popliteal vein with intraluminal filling femoral vein



Fig 3. Lung scintigram showing progression of the perfusion defects mainly on the right but also on the left side

vein of the left leg. The blood pressure was d physical examination of the heart and lungs as chest X-ray revealed normal findings. ECG on admission showed S_I–Q_{III} syndrome and a slight deviation indicating a right ventricular load disappeared during the following days. The condition improved during the first few days but he had moderate fever and slight chest pains at ...ation. Serial estimations showed slight in... a S-ASAT (0.56–1.44 μkat/l) and S-ALAT ...ably the upper normal limit in our laboratory ...r both enzymes. On the fifth day there was a ...optysis.

...scintigram showed a rather large perfusion de... ventral part of the right upper lobe (Fig. 1). A chest X-ray was still normal. Heparin and were given.

...am of the left lower extremity revealed a sac... ...sm, approximately 4.5 cm in diameter from the dorsal part of the popliteal vein and masses of thrombotic material with proximal of the thrombus into the distal part of the vein (Fig. 2).

...t was transferred to another hospital for A new lung scintigram showed progression of the defects in both lungs (Fig. 3). A venogram of the was normal. The aneurysm was resected and the closed with direct over and over suture. A new two days later showed complete obstruction of ... vein at the site of the aneurysm.

...ation on the fourth day a thrombus in the ... vein was resected by Fogarty technique and the s closed with a saphenous patch graft.

...ient was discharged on oral anticoagulant seven ...er the second operation. Lung scintigram after the ...m was normal. At six months follow-up he re...ed, has no recurrence of pulmonary embolism and ...ptoms from his postthrombotic leg.

DISCUSSION

This patient presented with acute pulmonary embolism and superficial thrombophlebitis of the left leg. However this was not the source of embolism but a venogram revealed an aneurysm of the popliteal vein which was clinically unsuspected. A lung scintigram supported the diagnosis of pulmonary embolism.

Anomalies of the deep veins of the lower extremities are rare and usually unilateral (2) and this is to our knowledge the second case described with pulmonary embolism secondary to unsuspected aneurysm of the popliteal vein (4).

Pulmonary embolism constitutes a very important cause of morbidity and mortality and so far venography is the only single most useful investigation in diagnosing suspected deep vein thrombosis (5). This method is helpful not only in outlining the site and extent of the thrombus but also in the decision about surgical intervention. Other common tests such as fibrinogen scanning and plethysmography can only diagnose a thrombus but are of no help in accurately outlining the source of embolism if it is a vascular malformation.

In patients with migrating superficial thrombophlebitis deep vein thrombosis occurs simultaneously in about 20% (6) why we recommend a venogram in these cases.

In patients with clinical symptoms of pulmonary embolism a chest X ray is usually normal like in

our patient and does not exclude this diagnosis A positive perfusion lung scintigram in combination with a normal chest X ray gives an accurate diagnosis

The postoperative result with secondary thrombosis in the popliteal vein was identical to the case referred to (4) A temporary arteriovenous fistula distal to the venous reconstruction should probably have been employed in the first operation in order to increase flow and prevent rethrombosis We have used that principle with encouraging results in more than 90 cases with acute iliofemoral menous thrombosis

This case strongly stresses the importance of perfusion lung scanning in patients with clinical signs of pulmonary embolism and of venography in cases of pulmonary embolism of obscure origin Venous reconstruction probably with a temporary arteriovenous fistula will prevent further embolism

REFERENCES

1 Breckenridge R T & Ratnoff O D [illegible] bolism and unexpected death [illegible] persons N Engl J Med Feb 6 [illegible] 19[illegible]
2 Browse N L The veins In [illegible] surgery (ed M Birnstingl) p 1[illegible]7 [illegible] don 1973
3 Dalen J E & Alpert J S Natural [illegible] nary embolism Prog Cardiovasc Dis [illegible]
4 Federman J Anderson S T Rosenbaum [illegible] Pitt A Pulmonary embolism secondary to [illegible] of deep venous system of the leg Br Heart [illegible] 1977
5 Kakkar V V Deep vein thrombosis [illegible] prevention Circulation 51 8 19[illegible]
6 Petroupolos P Enderly J B [illegible] Hahnloser P The risk of lung embol[illegible] thrombosis of the vena saphena magna [illegible] 5–6 797 19[illegible]8

Acta Med Scand 208 411–415 1980

Multiple Myeloma and Gastric Carcinoma

Possible Late Effects of Limited Abdominal X Irradiation

Marion Peters and Ian R Mackay

From the Clinical Research Unit of Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital Victoria Australia

CT A man, aged 34, was treated in 1954 ulcer by antroduodenectomy followed diation to the stomach in a dose of 2000 two decades he developed several condi butable to the previous irradiation, includ hysical appearances of premature ageing, of the left kidney due to irradiation ne immune deficiency, multiple meyloma of and lastly, carcinoma of the stomach The especially the left, the bone marrow and would have been in the field of X irradia effects of local X irradiation are discussed n to the known effects of total body irradia ausing decreased longevity in animals and cancer in man

f myeloma gastric carcinoma X irradiation phritis

Scand 208 411 1980

g term deleterious effects of low doses of radiation in man are attracting considerable Persuasive evidence has come from obser on the occurrence of cancer in persons giv peutic irradiation for various benign condi exemplified by an excess of leukaemia and na of the lung and stomach after irradiation ylosing spondylitis (3) and in Japanese ons exposed to nuclear bomb irradiation

unit has kept under surveillance a group of who were given limited X irradiation dur 0–60 to reduce gastric acidity as a therapy ic ulcer (23) This case report records a uni up of degenerative and neoplastic conditions ddle aged man 10–20 years after irradiation ssibly attributable to this

CASE REPORT

In 1954 a male patient aged 34 presented with epigastric pain due to duodenal ulcer of several years duration After unsuccessful medical treatment he was treated surgically by antroduodenectomy followed three weeks later by X irradiation in an estimated dose of 2000 rads The stomach was irradiated through anterior and posterior portals in the left upper quadrant of the abdomen as described by Scott et al (23) Thereafter he remained free of symptoms of duodenal ulcer

In 1964 investigations revealed mildly impaired renal function blood urea 7 5 mmol/l (normal laboratory range 2 5–8 3) creatinine clearance 74 ml/min (normal laboratory range 90–150) Also in 1964 an observation in the case record noted that he appeared prematurely aged in relation to his chronological age of 44 years and a peroral biopsy of the gastric remnant showed chronic atrophic gastritis marked by a heavy infiltration of lymphocytes and plasma cells and glandular atrophy In 1972 he had evidence of benign prostatic hypertrophy for which trans urethral resection of the prostate was performed and intermittent claudication in both legs after walking 200 yards Renal function tests again showed mild impairment and an i v pyelogram showed functioning kidneys the left measuring only 11 cm in length and the right 12 cm The physical appearances of premature ageing were again noted Immunological function tests for cell mediated immunity included delayed type hypersensitivity responses to five ubiquitous antigens and induction of sensitization to DNCB (13) these showed non reactivity

In 1973 the patient complained of back pain X ray examination revealed osteolytic lesions in both femora left humerus and skull and degenerative changes in the lumbosacral spine Serum electrophoresis revealed a low level of IgM and a paraprotein identified as being of IgA class with lambda light chains Other investigations consistent with multiple myeloma revealed an ESR of 104 mm/hour Bence Jones protein in the urine a Hb level of 10 9 g/100 ml with a normochromic normocytic blood film and a bone marrow aspirate containing 29% plasma cells Renal function had further deteriorated the blood urea then being 13 7 mmol/l and the creatinine clearance 12 ml/min A barium meal X ray examination suggested an abnormality at the anastomotic site but gastroscopy



Fig 1 Physical appearance of the patient at age 57 considered to represent a prematurely aged man

showed only mild narrowing at this site and multiple biopsies showed chronic atrophic gastritis

The multiple myeloma was treated with cycles of cytotoxic drugs melphalan 12 mg/day and prednisolone

1 0 mg/day for four days and pr... for six days) repeated e... Between 1964 and 1975 there we ... nary infection

In 1976 the patient presented with epigastric pain and anorexia and ... erably older than his 57 years (Fig 1) ... examination showed a gas... cally resected. Post opera... ch pneumonia The operat... cancer at the anastom... ly was a mucin producing adenocarcinoma ... atrophic gastritis in the ga...

Abnormal findings at a limited ... bronchopneumonia a shrunken left kidney ... and a normal sized right kidney ... sclerosis microscopically of the med... arteries arcuate arteries and ... kidney with changes of benign nephro... right kidney and no evidence of metast... gastric carcinoma

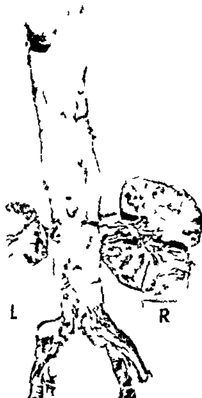
DISCUSSION

The patient described here was treated for ... ulcer by antroduodenectomy and ... radiation to the left upper quadrant ... in a dose of approximately 2000 rads ... peptic ulcer by gastric irradiation was ... Ricketts et al in 1948 (19) and was used ... with surgery in this unit in 1953 ... being 1 500-3000 rads Left sided renal ... described by Thompson et al (25) ... long term surveillance of the irradiated ...

After partial gastrectomy and irradia...



Fig ... Gastric ... ...



dneys obtained post mortem from patient show all shrunken left kidney presumably resulting ation to left kidney 22 years previously

ained well for over 10 years but then de a sequence of conditions which might be d to antecedent irradiation The first ab- es noted on routine follow up were mild nt of renal function and physical appear premature ageing Two neoplastic condi ultiple myeloma and carcinoma of the developed thereafter and death occurred t operative infection at the age of 57 Pre geing admittedly is a wholly subjective as t as there are no accepted quantifiable in ageing but was independently noted by bservers Decline in cell mediated immune s is known to occur in advanced age (13) demonstrable in our patient at the age of 52 ffect of irradiation in accelerating natural has been reported in man and animals (2) t al (11) in a study on mice given varying f X rays found that longevity correlated ly with the early appearance of diseases as l with human ageing notably ... acts greying of hair and nephrosclerosis Conard et al (6) in a study on humans described acceleration of ageing processes by characteristics assessed on physical examination (7) in a Marshall Islands population exposed to fall out from atomic bomb tests accelerated ageing was considered to be a late effect of radiation and a manifestation of non repairable injury Anderson et al (1) reported a reduction in life span in survivors of the Hiroshima and Nagasaki atomic bombs especially evident in those irradiated at an early age Among atomic bomb survivors according to Jablon (12) premature deaths were due entirely to cancers and if such causes were excluded no non specific life shortening effect was evident All of these reports however related to total body irradiation and there is no information on decreased longevity attributable to local irradiation

Gastric irradiation causing left sided nephritis has been previously reported from this unit (25) and is further exemplified by the present case abnormal renal function being detected on routine follow up 10 years after irradiation and shrinkage of the left kidney being shown later by i v pyelography The unilateral shrinkage of the left kidney found at autopsy together with suggestive vascular damage (20 25) indicated that radiation damage was responsible It is recognised that unilateral radiation nephritis should not prejudice renal function but there were less advanced arteriosclerotic changes in the right kidney possibly attributable to scattering of the X ray beam

The effect of irradiation in inducing neoplasia is well established Brown and Doll (3) reporting on 14 000 patients given radiotherapy to the spine for ankylosing spondylitis found a marked increase in leukaemia aplastic anaemia and cancers especially of the lung stomach and lymphoreticular system The highest frequency of cancer in the above study (7) was in the more heavily irradiated sites and cancer increased with increasing time from irradiation rising to twice the expected incidence 9–14 years after radiotherapy Thyroid cancer is a well known complication of antecedent irradiation to the head and neck (24) In addition irradiation from atomic explosions in Japan is incriminated as a cause of various cancers (12 26) Although cancer of the stomach is not usually included among cancers induced by atom bomb irradiation perhaps because the prevailing high incidence of gastric carcinoma in Japan obscures such an increase

ANNOUNCEMENTS

The Twentieth Second Postgraduate Institute for Pathologists in Clinical Cytopathology is to be given at The Johns Hopkins University School of Medicine and the Johns Hopkins Hospital Baltimore Maryland USA March 22–April 3 1981. The entire course is given in English. The full two-week program is designed for pathologists who are certified (or qualified) by the American Board of Pathology (PA) or their international equivalents.

Applications is to be made before Jan 8 1981. For details write John K. Frost M.D. 610 Pathology Building The Johns Hopkins Hospital Baltimore Maryland 21 05 USA.

RIA 81 Advanced ... ur e n Monoclonal Antibodies and ... Lur sen t e I ... ro ssa n Human Diagnosis and Monitoring of Therapy May 6–7 1981 and *3rd International Symposium on Calc te p c Hor nes Methods and Clinical Applications* May 8–9 1981 will be held in Gardone Riviera Italy.

Deadline for receipt of abstracts Feb 15 1981.

Organizing Secretariat Fondazione Giovanni Lorenzini Via Monte Napoleone 23 1 0121 Milan Italy.

The 2nd International Symposium on S ... t stat n sponsored by the Serono Symposia International will take place in Athens Greece June 1 3 1981. This meeting will include invited lectures and a limited number of free communications. Congress language is English.

Deadline for receipt of abstracts (max 250 words) Jan 15 1981.

Further information Pr E S Rap... M D ... Center and Artificial Pan cas L ... De ... Clinical Therapeutics Athens Un ... P O B... Athens 606 Greece.

International Symposium on L... Lip oxygen e Products will be held ... June 10–12 1981.

Scientific communications ... the subject of the meeting will be considered by the ... tific Committee. Deadline for receipt (in English) Feb 15 1981.

Information Organizing Secretariat F... Giovanni Lorenzini Via Monte Napoleone ... Milan Italy.

International Symposium on C... ... *New trends in Surgical and Me...* ... in Gardone Riviera (Garda Lake) Italy ...

Deadline for receipt of abstracts ... March 1 ...

Organizing Secretariat Fondazione G... Lorenzini Via Monte Napoleone 23 1 20121 M...

12th International Congress of Chemotherapy ... held in Florence Italy July 19–[illegible] 1981.

Topics Antimicrobial, antican... and ... therapy as well as immunology and ...

Deadline for abstracts Feb 15 1981.

Further information Secretariat 12th ... Congress of Chemotherapy Via de ... Florence Italy.

Acta Med Scand 208 417–423 1980

Bacteriuria in a Population Sample of Women

Prevalence Characteristics Results of Treatment and Prognosis

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ACT The prevalence of bacteriuria was in a population sample of women aged 38–60 ant (≥100 000 bacteria/ml of the same species consecutive specimens) or probable bac (≥100 000 in the first and 20 000–90 000 bac of the same organism in the second speci were found in 5% of the women, increasing 5% in women aged 38 to 8 6% in women aged herichia coli predominated (90% of those with ant bacteriuria), and 91% of the Escherichia rains were sensitive to sulphonamides About the women who were non bacteriuric after erm treatment had one or more recurrent uri ract infections during a two-year follow up Serum creatinine and urine concentrating y did not differentiate women with signifi r probable bacteriuria from the others ogical radiological changes were found in 17% teriuric women who were submitted to i v raphy When re-examined six years after the tudy 23% of initially bacteriuric and 5% of y non-bacteriuric women had bacteriuria Pa with renal lesions have been followed for ten but none of them has developed progressive impairment Three women with chronic py hritis and acute pyelonephritic attacks in the ere discovered when screening the concentrat pacity in this population sample but they were cteriuric when screening for bacteriuria A of this kind must be conducted over many years valid conclusions can be drawn

rds population study women bacteriuria renal n prognosis

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ons of screening for bacteriuria in non preg- women are contradictory Many investigators rt the view that search for asymptomatic bac a is hardly of preventive value and that term treatment suitable for large scale use is ineffective (1 18) Furthermore the prognosis for non pregnant women with asymptomatic bac teriuria is generally good However the natural course of bacteriuria in the long run is still un known and the natural history of chronic py elonephritis is enigmatic There is still no certain way of detecting the minority of patients who are at risk of renal damage Until a test to identify these patients has been developed as wanted by O Grady (14) and others it seems important that longitudinal studies are prolonged over many years

We report on the prevalence of bacteriuria in a population sample of women initially studied in 1968–69 The screening was part of a comprehen sive project including hematological cardiovascu lar metabolic gynecologic and psychiatric studies This study gives an account of the types of bacteria symptoms results of treatment and incidence of recurrent infections The majority of women were re investigated after 6 years in 1974–75 and those with repeated infections and/or renal lesions have been followed for ten years

STUDY POPULATION

A population study of women in five age strata (38 46 50 54 and 60 years) was carried out in Goteborg Sweden during 1968–69 (3) Altogether 1462 women participated (90 1% of those sampled) Further details of the sampling procedure and characteristics of the non-participants have been published earlier (3) The way of sampling ensured that the women were representative of the female popula tion of Goteborg in the ages studied

Six years later in 1974–75 the same population sample was re studied On this occasion 1302 women partici pated which means 89% of the participants in the first study Further details of the second study are given elsewhere (4)

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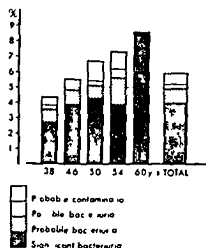


Fig 1 Prevalence of bacteriuria in a population sample of women The broad line denotes those who received treatment

METHODS

In both stud es the women were asked to come n the fasting state in the morn ng and were exam ned at various stat ons n a fixed order (3 4) They had been asked not to void urine at home if poss ble Clean vo ded m dstream urine spec mens were kept in a refrigerator unt l cultured n the Bacteriolog cal Laboratory with n six hours A 0 003 ml urine sample was streaked twice on a blood agar plate w th a cal brated loop and 0 05 ml were spread on a plate of lactose bromthymol blue (mod fed Drigalski) agar (10) Counts of Escherich a coli and other Enterobacteriaceae could be est mated to a lower l mit of 70/ml When the plates were crowded the urine sample was recultured quantitat vely after serial d lut on A s mpl fied O-sero-group ng (11 12) was performed on all E coli stra ns wh ch were saved as deep agar stab cultures under sterile paraff n o l in the dark Ant b otic sens tivity tests were performed by a s ngle d sc agar d ffus on method (6)

Women were regarded as non bacteriuric f the r urine spec men conta ned 0 000 gram negative rod bacteria or 100 000 gram pos tive bacteria per ml The others delivered at least one add t onal ur ne spec men 7 10 days er the f rst test

Four categories of bacteriuria were def ned 1) S gn f cant bacteriuria two spec mens each conta n ng ≥100 000 ba teria/ml of the same E coli O-group or of the same pec es f other than E coli or a s ngle specimen conta n ng ≥100 000 bacter a/ml s multaneously w th symptoms of urinary tract nfect n requ r ng mmed ate treatment 2) Probable bacteriuria one spec men w th ≥100 000 and another with 0000–90 000 bacteria/ml of the same organism as def ned above 3) Poss ble bacteriur a one spec men w th ≥100 000 and another w th 0 000 ba teria/ml of the same organ sm or ≥ 0 000 of a d fferent organism 4) Probable contaminat on ne pe men w th ≥100 000 and another w th 100 000 bacteria/ml of gram-pos tive organisms belonging to the normal urethral and genital flora.

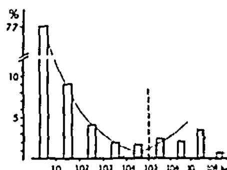


Fig 2 D stribut n of E c li c unts n 1650 mens from the f rst 1440 women studied

W men w th s gn f ant r pr bable ba treated with tablets contain ng 0 25 g su pha 0 1 g sulphamethoxypyridaz ne (Sulfapral® ta lets b i d for ten days Women who had p e per enced adverse react ons from su phona en 0 5 g amp ll n (Doktacillin® A ra) four for five days followed by 0 05 g n trofura tin® Pharmacia) t i d for ten days Urine re then exam ned at scheduled regular n e years

St st c l m th ds Conven nal me ho for calculat ng mean values and s a ard (S D) The hypothe is of no differences betw was tested w th the χ^2 te t

RESULTS

Prevalence of b cter r a

The prevalences of all categor es of bac shown in Fig 1 In the total sample women had s gn f c nt r pr bab e b The prevalence of gn ficant ba teriu with age (Table I) ... en had significant bacteriuria In half of en with probable b cteriuria a th d contained ≥100 000 bacteria ml

Table I *Prevalence f s g f ca t a d b cter r a*

Age (yr)	Total sample	Significant bacter n
38	3 2	
46	431	
50	378	
54	180	
60	81	
Total	1 462	

ll Bacterial findings

	n	%
ant bacteriuria (n = 58)		
erichia coli	52	90
ella	2	3
us	1	2
ylococcus coagulase negative	2	3
nebacterium vaginale	1	2
e bacteriuria (n = 13)		
erichia coli	12	92
us	1	8
bacteriuria (n = 4)		
erichia coli	4	100
le contamination (n = 11)		
a streptococcus	4	36
ococcus	1	9
ylococcus coagulase negative	1	9
bacillus	3	27
nebacterium vaginale	1	9
heroid rods	1	9

ology

acterial findings are listed in Table II E coli und in 90% of the women with significant 92% of those with probable bacteriuria distribution of E coli per ml of urine in 1 650 ens from the first 1 440 women is shown in Two peaks are recognized one of non in but contaminated specimens the other of d specimens Less than 2% of the specimens coli counts of 10 000–100 000/ml

of the 68 strains of Enterobacteriaceae caus cteriuria for which treatment was given 91% sensitive to sulphonamides (Table III) Three six women with sulphonamide resistant E ad recently been treated with sulphonamides current urinary tract infections

lts of treatment

t term follow up We treated 67 of 71 women in way described Three of them were given sul amide in spite of their sulphonamide resistant ria Four women were treated elsewhere A ure one week after treatment on urine samples 1 65 of these 67 women revealed that seven % of those checked) were still bacteriuric six es containing E coli and one enterococci One oli strain was sensitive to sulphonamides and were resistant one already before treatment o of three sulphonamide resistant strains had ppeared after 12 days of sulphonamide treat nt

Table III *Sensitivity of gram negative bacilli to sulphonamides in women with significant or probable bacteriuria*

	n	%
E coli	58/64	91
Klebsiella	2/2	100
Proteus	2/2	100

Long term follow up In addition to the examination about one week after treatment the women were checked up after 3 6 9 12 18 and 24 months The cumulative frequency of recurrent infection is shown in Fig 3 *Four women who did not attend all* follow up examinations and those seven who had infected urine shortly after treatment are not included in the figure This means that 56 women who were non bacteriuric after treatment were followed up for two years or until infection re appeared About half of these women (52%) became bacteriuric (≥100 000 bacteria/ml) on at least one occasion during the period Including those with bacteriuria shortly after treatment and two women who were not checked up until about six months after treatment 38 (58%) of 65 women initially treated and followed up had persistent bacteriuria or recurrent infection

Side effects of antibacterial treatment Three (5%) of 65 women infected with sulphonamide sensitive bacteria reported previous side effects of treatment with sulphonamides Four (6%) reported abdominal pain dysuria or discomfort during sulphonamide treatment These symptoms were however hardly due to the sulphonamide treatment None of eight women treated with ampicillin and nitrofurantoin reported side-effects

Table IV *Urine concentrating capacity <700 mOsm/kg H_2O in women with bacteriuria (significant or probable) compared to the total population sample of women*

Age (y)	Women with bacteriuria n	%	Total population sample of women n	%
38	2/11	18	48/353	14
46	6/19	32	68/411	17
50	5/20	25	101/386	26
54	3/9	33	53/178	30
60	5/5	100	34/77	44

Table V *Abnormal radiological findings in the urinary tract of women with significant bacteriuria*

Pat no	Age (y)	Radiological findings	Bacteria of initial infection	Bacteria of recurrence
1	38	Renal hypoplasia and/or chronic pyelonephritis	E coli	Enterococcus
2	38	Renal calcification	E coli	
3	38	Renal stone	Proteus	Proteus
4	46	Vesico-ureteric reflux	Proteus	Proteus and E coli
5	46	Renal hypoplasia	E coli	E coli
6	50	Renal papillary necrosis	E coli	E coli
7	50	Renal scar (vascular?)	Staphylococcus coagulase negative	Klebsiella
8	54	Hydroureter	E coli	E coli

Six year re-examination A urine specimen was again examined in 1974–75 Out of the 67 women initially treated for bacteriuria 57 (85%) participated in the re-examination Thirteen (23%) had significant bacteriuria compared to 63 (5%) of those 1 236 who participated in the follow up study and who had initially not had significant or probable bacteriuria The difference was statistically significant ($p<0.001$)

Characteristics of women with significant or probable bacteriuria

Symptoms of urinary tract infection Seven (10%) of 71 women with bacteriuria defined as significant or probable reported dysuria Another four reported back pain located to the kidney region in two If the latter complaints are regarded as symptoms of urinary tract infection 11 women (15%) reported such symptoms

Renal function All women with significant or probable bacteriuria had serum creatinine values below the upper limit of the normal range (≤106 mol/l = 1.2 mg/100 ml)

A urine concentration test (osmolality during the 13th hour of thirst) (2) was performed in 64 women with significant or "probable" bacteriuria A maximum osmolality of <600 mOsm/kg H_2O was considered significantly decreased and led to further examination Of the 64 women participating in the test two had concentrations below this level One of these two women had a normal concentrating capacity after administration of pitressin (≥600 mOsm/kg H_2O) while the other had a decreased concentrating capacity also after pitressin and could thus be considered to have impaired tubular function

Twenty-one of the bacteriuric women had urine osmolality below 700 mOsm/kg H_2O during the 13th hour of thirst (Table IV) When compared with urine osmolality below this level the concentrating capacity tended to be lower in women with than without bacteriuria in some age strata but the difference was not significant

Results from i v pyelography During the follow up period 46 of the 67 women were subjected to i v pyelography Mainly those without recurrence of bacteriuria refused Pathological findings were found in 8 (17%) of the 46 women (Table V)

Leucocyte counts in the peripheral blood and ESR did not differ between women with significant or probable bacteriuria and other women in the population sample (Table VI)

Women with recurrent bacteriuria

Women in whom bacterial infections recurred after treatment were offered further control as outpatients at the Department of Nephrology. Of these 24 women had reduced concentrating capacity (<700 mOsm/kg H_2O after pitressin) ... five had borderline values (700–800 mOsm/...)

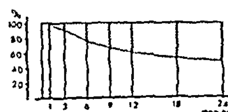


Fig 3 Long term follow up of 56 women treated for bacteriuria and free from bacteria after treatment Hatched area denotes recurrences white area no recurrences

1 *Leucocyte counts in peripheral blood and ESR in women with bacteriuria (significant and …) compared to the total population sample of women*

	Women with bacteriuria			Total population sample		
	n	Mean	S D	*n*	Mean	S D
n (10⁹/l)						
	13	5 7	1 6	363	5 6	1 8
	1	6 0	2 0	419	5 5	1 7
	0	5 5	2 1	395	5 3	1 6
	10	5 0	1 0	180	5 1	1 6
	7	5 2	1 5	81	5 2	1 7
m/h)						
	13	11 3	9 6	372	10 9	11 0
	1	10 [illegible]	6 7	431	11 0	8 4
	0	14 5	11 0	398	12 0	8 4
	10	13 1	8 9	180	15 5	15 0
	7	[illegible] 4	12 1	81	17 7	13 6

wo further cases of concentrating defect
ded to those found at the population screen

patients one of whom had normal concen
capacity had borderline values for serum
ne 106–120 μmol/l or 1 2–1 4 mg/100 ml
er patient had a unilateral small kidney and
iological picture and laboratory findings
d congenital hypoplasia
of these 24 women had pathological
gical findings (Table V) unilaterally reduced
size and blunted calyces in three one of
had also vesico ureteric reflux Micturation
aphy had not been performed in the others
tient had bilateral papillary necrosis In
three patients one kidney had double
a d ureters No calyceal changes but a kid
ir probably vascular was found in one pa
ne of the patients with reduced concentrat
acity had a normal urogram
patient developed hypertension which re
treatment Borderline blood pressures (dia
90–105 mmHg) were noted in two patients
n patients had further recurrences of bac
s in a few cases combined with symptoms
itis Antibacterial treatment was given re
ly Except for women with normal renal
n and normal radiological findings the pa
have been followed for up to ten years No
has demonstrated progressive renal impair
during this period The patient with renal
ry necrosis has developed increasing cavities
papillae She is suspected for analgesic abuse

DISCUSSION

An increasing prevalence of bacteriuria with increasing age and a marked predominance of E coli with a large majority of the strains being sensitive to sulphonamides was found in this study in agreement with results from previous studies of women (7 9 17)

The method of collecting and culturing urine specimens seemed to be very reliable at least as far as E coli is concerned The distribution of bacterial counts of E coli was similar to that achieved when catheterized specimens were used (8)

As in previous studies of bacteriuria the majority of bacteriuric women did not report any symptoms There were no differences in leucocyte counts or ESR between bacteriuric and non bacteriuric women indicating that the majority of women had no serious infection Similarly impaired renal function measured as serum creatinine or urine concentration capacity was not overrepresented in this group of women

At the 6-year follow up the prevalence of bacteriuria in the total sample of women was unchanged 5% whereas the corresponding percentage of women treated for initial bacteriuria was 23 Women with abnormal radiological findings seemed to be especially prone to new infections which has also been found in previous studies (16) Pathological radiological findings were detected in 8 women One woman had decreased concentration capacity although the i v pyelography was normal

It is interesting to compare these results with the outcome of the concentration screening performed

in the total population sample in 1968–69 (2) Eleven women had low urine osmolality even after a pitressin tannate test and renal disease was found in ten of them Two of them are identical with patients in the present study Three of the patients discovered by the concentration screening had a past history of acute pyelonephritis but were non bacteriuric at the time of the initial population study

Thus individuals with renal lesions probably due to earlier urinary tract infections may be missed in a population screening of bacteriuria However a general recommendation of simultaneous screening of bacteriuria and concentrating capacity seems not to be realistic A simple screening test for concentrating capacity e g overnight thirst gives many false positive results and must be followed by a more reliable test like the pitressin tannate test On the other hand several cases of early renal lesions are bound to be overseen by screening procedures

One aim of a cross sectional population study is to find out how many of the bacteriuric individuals have pre-existing renal lesions Here a clinical concentration test can be used to select patients for i v pyelography

Another and certainly an important aim is to establish a base for longitudinal studies of the consequences of bacteriuria It is of interest to define the consequences in patients with as well as without initial lesions A clinical long term study in Goteborg has demonstrated that frequent recurrences of urinary tract infections accelerate the progress of renal insufficiency in chronic pyelonephritis (5) The majority of patients with clinical and radiological picture of chronic pyelonephritis and with renal function reduced to about 50% often demonstrated a very slow progress over a decade) There is no reason to believe that the progress ould be faster before the function is reduced to 50% Thus five years is a short period in a population study and even a 10-year period is certainly not long enough It is reasonable that a population study of bacteriuria should cover many years before valid conclusions can be drawn

According to several investigators bacteriuria should not cause renal scars after the age of four (13 15) However when diagnosing scarred kidneys and vesico-ureteric reflux in 55- or 60-year-old women it does not seem indisputable that they should have acquired these changes in early childhood

The next examination of the pres[illegible] sample is planned to take pla[illegible] low up in 1980–81 The indications [illegible] be discussed in a later communication [illegible] report on the serological O grouping [illegible] strains

At present we restrict the conclusions [illegible] commendation that bacteriuric women [illegible] submitted to a concentrating test [illegible] defect an unfavourable resistance pattern [illegible] bacteria Proteus and recurrent symptom[illegible] tions are indications for i v pyelogra[illegible] cystoscopy

REFERENCES

1 Asscher A W Sussman M Waters W E [illegible] J A S Campbell H Evans K T & W[illegible] [illegible] Asymptomatic signifi ant bacteriuria [illegible] pregnant woman II Response to [illegible] low-up Br Med J 1 804 1969
2 Bengtsson C & Bengtsson L [illegible] capacity in women the results of a [illegible] in a population study Clin Nephrol 6 [illegible]
3 Bengtsson C Blohmé G Hallberg L [illegible] T Isaksson B Korsan-Bengtsen K [illegible] Tibblin E Tibblin G & Westerberg H [illegible] of women in Gothenburg 1968–69 [illegible] study General design purpose and [illegible] Acta Med Scand 193 311 1973
4 Bengtsson C Hallberg L Ha[illegible] A Isaksson B Lennartsson J L[illegible] Lindstedt S Noppa H Rod[illegible] S The population study of women [illegible] 1974–1975—the second phase of a l[illegible] General design purpose and sampl[illegible] J Soc Med 6 49 1978
5 Bengtsson U Long term pat[illegible] elonephritis Contrib Nephrol 16 31 1979
6 Ericsson H & Sherris J [illegible] ing Acta Pathol Microbiol Scand [illegible] 1971
7 Evans D A Williams D [illegible] Miao L Warren J W Her[illegible] da J Chapman W G R[illegible] Bacteriuria in a popula[illegible] J Infect Dis 138 768 1978
8 Kass E H Asymptom[illegible] tract Trans Assoc Am[illegible]
9 Kass E H Savage [illegible] The signifi ance [illegible] medicine In Prog[illegible] Kass) pp 3–10 Das[illegible]
10 Kauffman F The [illegible] ceae Munksgaard
11 Lidin-Janson G [illegible] Lanson K O[illegible] Escherichia [illegible] dren J Med M[illegible]

..on K Lidin-Janson G & Winberg J Resist ...nary infections resulting from changes in resist ...tern of faecal flora induced by sulphonamide ...mal environment Br Med J 3 305 1970

... M S F Meller S Verrier Jones R ... A Fletcher E Mayon White R Leding ... Smith J & Jonston H Urinary tract in ...rls with covert bacteriuria Arch Dis Child 50 ...75

... F Urinary tract infection in women J R ...sicians 13 70 1979

... G L Maling T M J & Hodson C J ...teral reflux and the scarred kidney Arch Dis ...49 531 1974

...an M Asscher A W Waters W E Evans J A S Campbell H Evans K T & Williams J E Asymptomatic significant bacteriuria in the non pregnant woman I Description of a population Br Med J 1 799 1969

17 Takala J Jousimies H & Sievers K Screening for and treatment of bacteriuria in a middle aged female population I The prevalence of bacteriuria urinary tract infections under treatment and symptoms of urinary tract infections in the Sakyla Koylio project Acta Med Scand 202 69 1977

18 — Screening for and treatment of bacteriuria in a middle aged female population *II Results of short term nitrofurantoin therapy and one year follow up* Acta Med Scand 202 75 1977

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Occurrence of Adult Fanconi Syndrome in Benign Monoclonal Gammopathy

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ΓT Adult Fanconi syndrome has been a manifestation of a latent form of my Since benign monoclonal gammopathy (BMG) t form of myeloma we studied ten patients s disease with respect to the adult Fanconi These patients were selected from a larger with BMG because of urinary excretion of l light chains In no instance could a com ancom syndrome be shown, but one patient, diabetic nephropathy, had very high f urinary β_2-microglobulins Two additional howed minor features included in the adult ndrome BMG does not seem to be associ th an increased risk of developing adult Fan ndrome

ds ben gn monoclonal gammopathy adult Fan d ome

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esence of urinary monoclonal light chains Jones proteinuria) in patients with some plasma cell dyscrasia has been linked to im renal function (21) Consequently the renal in these patients has been regarded as an t man festation of the disease with relation sis

eased amount of monoclonal light chains r ne of pat ents with multiple myeloma may mpaired renal function and secondary hy mia. It has been proposed that monoclonal l ght cha ns especially those of kappa type e a role in the development of renal tubular d dysfunction so that features suggestive ed adult Fanconi syndrome appear (20) syndrome in adults has been reported in on with multiple myeloma amyloidosis ce Jones proteinuria (7 8 11 15 16) In eports the diagnosis of renal tubular dysfunc preceded the development of multiple ma or amyloidosis never the reverse (8)

Patients with plasma cell dyscrasia and t Fanconi syndrome represent a distinct variant the monoclonal gammopathies characterized by slow growth of the tumor with early development of metabolic complications for example renal prox imal tubular dysfunction (20) Adult Fanconi syn drome is defined as a dysfunct on of t proximal renal tubules resulting in vitamin D resistant osteo-malacia glucosuria generalized aminoaciduria hypophosphatemia chronic acid si and hypopo tassemia (16)

Since adult Fanconi syndrome has been de scribed as preceding myelomatosis or a ccompany ing plasmacytic dyscrasia with mild plasm cyt sis one would suspect that it could als be as sociated with benign monoclonal gammaopathy (BMG) which is in essence a premyelomatous con dition and not infrequently associated with excr tion of monoclonal light chains in the urine (18) Therefore we decided to study a group of patients with BMG with respect to adult Fanconi sydrome We chose to select those among 45 patients with BMG who—in addition to plasma M component—had Bence Jones proteinuria We also thought that this could have therapeutic implications perhaps one could identify a subgroup of BMG patients at risk prone to develop renal proximal tubular dys function These patients could then be treated in an earlier phase of their disease (1 10 22) to prevent excessive production of monoclonal light chains and subsequent tubular dysfunction

PATIENTS

We studied 10 patients 6 men and 4 women mean age 74 years (range 62–88) classified as having BMG The cri teria for classification are published elsewhere (18) All ten patients excreted light chains in the urine in various quantities (Table I) The duration of the disease varied from 9 months to 16 years (mean 4 5 years)

ponents sho ed a d fferent electro- pot s f om those of the corre pond ng Jwe e den fed w th the a d of immuno e s as m noclonal kappa or lambda Se en Bence Jones prote ns were of kappa f lambda type Calculated quantities of J es pro e n varied from 60 to 570 mg/l ert (no 5) excreted more than 7000 mg/l al mmun globul n cons sting of the M-component and a smaller amount of al k ppa cha ns Th s patient al o had m u w h d abet c nephropathy E ght had low plasma concentrations of un n background mmunoglobul ns

u

en s excreted n reased amounts of ami in the u ne wh le seven had normal val

n l(l t
nd u b t

nts w h BMG had normal serum concen of pho pha e and calc um Four had a sl ght n of album n concentrat on Serum con s of sod um and potass um were normal s

n n f l ose

na def ned as 24-hour excret on exceed ng was observed n two patients (one was a

d f a n

p ent showed a ur ne pH below the range of 4 7 On the same occas on his se carbona e concentrat on was 21 mmol/l range 4-32)

DISCUSSION

been shown that prolonged excret on n the monoclonal l ght cha ns—part cularly kap- w hout ev dence of def n te mult ple a may g e r se to adult Fancon syndrome E perimental ev dence (4) ndicates that the to the prox mal tubule cells n the k dney s p o onged reabsorpt on in these cells of n f red n the glomerulus The k dney is e of catabol sm of l ght cha ns wh ch was by Wochner et al (25) who stud ed the fate of radioiod nated Bence Jones prote n n n hr tomized ureter severed mice They l active end genous catabol sm was h m in overall Bence Jones metabol m e as prote nuri accounted for less th n total n etabol sm It is theref re prolonged overload of the k dneys t chains may dam ge the cells r sp bl catabolism wh ch re most l kely prox mal tubular cells

Several cases of adult Fancon sy been reported to occur n s c fest myeloma (8 16 0 In a l n drom e has preceded the nse o

Since it has been ho vn l f premyelomatous cond t n with excret on of m n l urine (14 18) t could be h patients are at r sk of syndrome Maldon d e tients w th Fanconi ynd l te nuria have a d st nct t p l characterized by a l p c This type of slo sly pr gr n p n s a is also typ cal for BMG t uld f that the same type f compl on n Fanconi syndrome ou d al t nd BMG For th s reason e de ded t ou patients with BMG who al o sh wed Ben prote nuria w th respect to Fa n synd om patients were selected among 45 th BMG Th were all essent ally well w th no c n om tant d s ease except for one who had d abetes mell tus and d abet c nephropathy

Our study sho vs that patient s th BMG do not run a h gh risk of develop ng Fancon syndrome one pat ent (no 5) showed incompletely developed Fancon syndrome th exce s ve excret on of β m croglobul n and am noac dur a However s nce this pat ent also has d abet c nephropathy (proven by kidney biopsy) it cannot be ma nta ned that the Fanconi syndrome is due exclu ively to the urinary excretion of monoclonal l ght chains Ava lable data (23) nd cate that poor metabol c control in pat ents w th d abetes somet mes may cause ncreased β m croglobul ns in the urine We therefore bel e e that the part al Fanconi syndrome ob erved n th s part cular case has a dual et ology d abet c nephro- pathy and pronounced excret on of monoclonal mmunoglobul ns as part of a BMG This pat ent excreted kappa cha ns and complete IgG M-com

ponent which was the major part of the excretion (Table I) Two additional BMG patients had incomplete Fanconi syndrome one of them (no 7) had elevated levels of β_2-microglobulin and blood urea and a decreased creatinine clearance the other (no 6) had slight aminoaciduria elevated blood urea and a decreased creatinine clearance

Our conclusion is therefore that patients with BMG usually do not develop adult Fanconi syndrome The reason for this is the usually low grade of Bence Jones proteinuria Patients who have developed Fanconi syndrome in conjunction with plasma cell dyscrasia have usually had several grams of monoclonal light chains per liter urine There are however exceptions to this general rule both BMG patients in our series who showed a partial Fanconi syndrome (nos 6 and 7) had low grade Bence Jones proteinuria (60 and 190 mg/l respectively) The partial Fanconi syndrome in case 7 consisted mainly of markedly elevated excretion of β_2 microglobulin while in case 6 this diagnosis was based mainly on a slight elevation of amino acids in the urine Interestingly patient 6 excreted lambda type light chains which has not previously been described in conjunction with adult Fanconi syndrome

From a therapeutic point of view we feel that treatment with cytostatics and corticoids is not indicated in patients with BMG even if they have a low grade (500 mg/l or less) Bence Jones proteinuria But if the excretion exceeds that level and if the patient also shows evidence of Fanconi syndrome it would be logical to start such treatment since it could reduce the risk of permanent tubular cell damage

REFERENCES

1 Alexanian R Haut A Khan A U Lane M Mckelvey E M Migliore P J Stuckey W J & Wilson H Treatment for multiple myeloma Combination chemotherapy with different melphalan dose regimens JAMA 208 1680 1969
2 Berggård I & Bearn A G Isolation and properties of a low molecular weight beta$_2$-globulin occurring in human biological fluids J Biol Chem 243 4095 1968
3 Chasson A L Grady H J & Stanley A Determination of creatinine by means of automatic chemical analysis Am J Clin Pathol 35 83 1961
4 Clyne D H Brendstrup L & First M R Renal effects of intraperitoneal kappa chain injection induction of crystals in renal tubular cells Lab Invest 31 131 1974
5 Coburn H J & Carrol J J Improved manual and automated colorimetri determination of se cose with use of hexokinase and glu phate dehydrogenase Cl n Chem 19 127 19
6 Ervin P E & Wibell L The serum level nary excretion of beta$_2$ microgl bul n healthy subjects Scand J Cl n Lab Invest
7 Finkel P N Kronenberg K Pesce A J V E & Pirani C L Adult Fanconi s amyloidosis and marked kappa-l ght chain pr Nephron 10 1 1973
8 Harrison J F & Blainey J D Adult Fan drome with monoclonal abnormality of globulin l ght chain J Clin Pathol 0 4 19
9 Henry R J Cannon D C & Winkelma Clinical chemistry Principles and techn ed p 1538 Harper & Row Hagerstow land 1974
10 Hoogstraten B Costa G Guttner J Fa Leone L A Harley J B & Glidewell O mittent melphalan therapy in multiple m JAMA 209 251 1969
11 Isobe T & Osserman E F Patterns of am and their association with plasma cell d monoclonal immunoglobul ns and Bence Jo teins N Engl J Med 290 473 1974
12 Johansson B G Agarose gel electrophoresi J Clin Lab Invest (Suppl) 124 7 197
13 Kampmann J P Siersbæk Nielsen K Kr M & Molholm Hansen J Aldersbetinget ner i urinkreatinine og endogen kreatinin Ugeskr Laeger 133 2369 1971
14 Kyle R A Monoclonal gammapathy of u mined significance—natural history in 241 ca J Med 64 814 1978
15 Kyle R A Maldonado J E & Bayrd E I pathic Bence Jones proteinuria—a d stinct ent J Med 55 222 1973
16 Lee D B N Drinkard J P Rosen V J nick H C The adult Fanconi syndrome C tions on etiology morphology renal f nct mineral metabolism in three patients Med 107 1972
17 Lindstedt G & Lundberg P A Loss of proteinuria pattern during urine concentratio commercial membrane filter cell (M nicon B tem) Clin Chim Acta 56 125 1974
18 Lindstrom F D & Dahlstrom U Mu ple or benign monoclonal gammapathy (BMG) differential diagnostic criteria in 44 cases o Clin Immunol Immun pathol 10 168 19
19 Lizana J & Hellsing K Polymer enhance automated immunol gical nephel metric ana illustrated by determination of urinary albu Chem 20 415 1974
20 Maldonado J E Velosa J A Kyle R A ner R D Holley K E & Salassa R M syndrome in adults A man festation of a lat of myeloma Am J Med 58 354 1975
21 Martin D W Siegel R C & Smith L kidney in multiple myeloma Medical Staf ence University of California San Francisco Med 129 41 1978

J R. Athens J W Wintrobe M A. &
n ght G E. Melphalan and myeloma. Expe
with a low dose continuous regimen Ann
and 72 665 1970
S L & Deckert T. The effect of metabolic
ascular permeability to small and
in short term juvenile diabetes Dia
ca 12 161 1976

24 Saifer A Gerrenfeld S &
metric microdeterminations
logical fluids with the ninhyc
Acta 5 131 1960
25 Wochner R. D Strober W
The role of the kidney in
Jones proteins and immunogl
Med 126 607 1967

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Lymph Node Toxoplasmosis

Follow up of 237 Histologically Diagnosed and Serologically Verified Cases

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RACT The clinical features histology and fol lymph node toxoplasmosis are presented in of 237 histologically and serologically veri Lymph node toxoplasmosis is a disease symptoms and in most patients the en mph nodes were the only sign Three fourths patients were women and the majority were 40 years of age The clinical picture was not but suggestive features included a relatively tory, presence of the nodes in the neck and lymphocytosis in peripheral blood Histologi in the lymph nodes were characteristic important features were strong hyperplasia general structure with small groups of oid cells both in the paracortical area and in centers Strands of monocytoid cells found 80% of the cases with typical also had high antibody titers and in more % of the cases with high antibodies, the lymph presented a typical picture of toxoplasmosis revealed that lymph node toxoplas- The follow up revealed that lymph node txo- is a disease without complications nor is connection with malignant lymphomas

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ozoan Toxoplasma gondii is an intracellu ite that causes infections both in animals man (5 17 23) The orgnaism is widely dis almost throughout the world A significant ion of people have antibodies against Toxo- a as a sign of previous infection in Finland c and in the USA about 50% of the popula / 11)

most serious but rare form of toxoplasmosis genital intrauterine infection usually includ ephalitis Cerebral damage in the survivors on Fatal general infections have been re in immunosuppressed and cancer patients arely myocarditis myositis or uveitis may be ly manifestation of toxoplasmosis

Lymph node toxoplasmosis accounts for the great majority of infections caused by Toxoplasma gondii The disease was first reported in Scan dinavia by Gard and Magnusson (6) and later by other authors (8 22) The usual diagnostic method has been lymph node biopsy and subsequent anti body determinations Toxoplasmosis presents with special histological features in the enlarged lymph nodes Lymph node toxoplasmosis is usually a mild disease (22 25) Later development of Hodgkin s disease after a well documented case has however been reported (21) and a possible infectious etiology in Hodgkin s disease has been discussed (9)

The aim of this study was to assess lymph node toxoplasmosis and its prognosis in a larger material as well as its possible connection with later malig nant lymphomas

MATERIAL AND METHODS

Lymph nodes suspected of toxoplasmosis by a pathologist were collected from Finnish pathology laboratories during 1963–78 A total of 667 cases were found in which toxo- plasmosis was suggested or mentioned as a differential diagnosis by the pathologist (2–4 of all lymph nodes from different laboratories) The slides were re examined histologically without knowledge of the clinical or sero- logical data The previous histological criteria for toxo- plasmosis suggested by Piringer Kuchinka et al (14) and Saxen and Saxen (18) were employed

Four hundred and three cases showed the typical his tological picture of toxoplasmosis Serology was available in 303 cases In 237 cases the antibody titers were as- sessed high enough to admit the diagnosis of recent toxo- plasmosis (dye test titers ≥ 256 immunofluorescence (IF) titers ≥ 160 or complement fixation (CF) titers ≥ 16) These 237 histologically and serologically proved cases are analyzed in the following

There were 23 additional cases with histology of toxo- plasmosis but fully negative serology (dye test or IF ≤ 4 or CF < 8) In seven cases there were high antibody titers without typical histology To pick out cases with histology diverging from the usual 350 cases with positive serology

Abbreviations IF = immunofluorescence CF = complement fixation

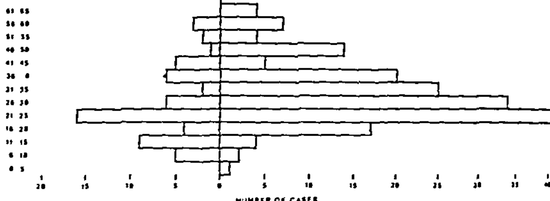


Fig 1 Age and sex distribution of the 237 cases of lymph node toxoplasmosis

(dye test ≥160 or CF ≥8) were checked for histology In addition to the 18 cases of typical toxoplasmosis already included three other cases were found Two were non specific hyperplasia, one was necrotizing granulomatous inflammation with positive tuberculosis culture Histological differential diagnoses will be treated in a forth coming paper

The clinical data were obtained from the hospital charts and serology was checked from the serological laboratories For comparison of the clinical data, 63 cases of non-specific hyperplasia with negative serology of toxoplasmosis were singled out from the basic material of 667 cases The patients were followed on the basis of hospital records when available In addition they were checked from the Population Registry of Finland for survival up to the end of 1977 and for possible later malignant lymphomas from the Finnish Cancer Registry up to the end of 1976

RESULTS

The age and sex distribution of the 237 patients is presented in Fig 1 Three fourths of the patients were women and three fourths were under 40 years of age The youngest patient was a 5 year-old girl the oldest a 63-year-old woman The mean age of the men was 27 5 years and of the women 31 6 years The cases were distributed all over Finland

Symptoms In the majority of cases the only symptoms were enlarged lymph nodes usually noted by the patients themselves The nodes were often initially tender and there was local pain in the adjacent structures Physicians discovered enlarged lymph nodes in five patients during their follow up for an unrelated disease Transient fever had been noted in 38 patients (16%) Mild symptoms resembling virus infection (sore throat tiredness and muscle pain) were often reported in the h[illegible] charts Three patients were hospitalized be[illegible] fever of unknown origin before the diag[illegible] five cases skin eruption was noted on the [illegible] nodes Muscle biopsy taken from one pa[illegible] muscle pains revealed myositis with sm[illegible] of epithelioid cells like those in lymph nod[illegible] plasmosis No other extranodal manifesta[illegible] toxoplasmosis were proved

Probably most of the lymph nodes were [illegible] to exclude the possibility of malignancy [illegible] the patients had been treated with an[illegible] out effect Only occasionally was toxop[illegible] suspected clinically

Lymph node enlargements The usual [illegible] (85%) was the head and neck region (Table [illegible] nodes were often situated behind the s[illegible]

Table I *Location of the excised lymph n[illegible]*

		Toxo-plasmosis (n=234)	Non-spec[illegible]
Head and neck		85	8
Anterior neck	54		
Posterior neck	27		
Supraclavicular	3		
Parotid region	1		
Axilla		11	14
Groin		3	[illegible]
Mammary glands		1	3
Other		–	
		(not indicated in 3 cases)	

II Duration of the lymph node enlargement

	Toxoplasmosis (%) (n=168)	Non specific hyperplasia (%) (n=43)
...weeks	11	9
...one month	28	14
...ths	34	19
...ths	21	18
...ths	2	5
...6 months	4	35
	(not indicated in 49 cases)	

Table III Maximal diameter of the enlarged lymph nodes

	Toxoplasmosis (%) (n=114)	Non specific hyperplasia (%) (n=36)
Less than 1 cm	18	33
1–2 cm	50	50
2–3 cm	25	11
3–4 cm	6	6
More than 4 cm	1	-
	(not indicated in 123 cases)	

...ideus muscle Axilla groin and the sub... ...f mammary glands were rare locations The ...h node enlargements were reported as ... in 25 cases (11% of cases with sufficient ... this respect) Chest X ray showed no ...d nodes in the pulmonary hili (45 cases X ray ... On average the nodes had been noted ...weeks but for less than four weeks in 44% ... cases (Table II) The majority of nodes were smaller than 3 cm in diameter (Table ...

...oratory examinations ESR was normal in ...f the cases and marked elevation (>20 mm/ ... noted in 10% Leucocytosis was exceptional ...ase) Relative lymphocytosis was the rule the ... of lymphocytes in the differential count ...ng 40% in 84% of the cases (Table IV) ...ils were not elevated In six cases atypi...mphocytes were reported in the differential ... Anemia was exceptional

...logy The antibody titers were usually meas...ior the first time soon after biopsy Already at ... titers were elevated in 216 (91%) of 237 ... whereas in 21 cases (9%) a fourfold rise was ... in sequential measurements Dye test/IF and ...ers correlated well in 80% of the cases but in ... (20%) the CF titers were low (≤8) when ...t or IF showed high titers (≥160) The exact ... of serological data is complicated by the ...nt scales used in different laboratories The ...Bunnel test for mononucleosis was negative or ... 30 cases but in one case the titer was 1 224 ...ly due to a double infection (toxoplasmosis ...onucleosis)

...atment Specific treatment (pyrimethamine 25 ... 1–2 plus sulfonamides e g sulfadiazine 500 ...) was given to 29 patients (12%) In three patients the treatment caused transient leucopenia Abortion was performed in three women because of suspected threat from toxoplasmosis to the fetus

Histology (Fig 2 Table V) In the serologically confirmed cases the histological picture was rather uniform The general structure was hyperplastic with abundant germinal centres and an active paracortical area As a specific feature there were groups of epithelioid like cells with abundant slightly eosinophilic cytoplasm Strands of monocytoid cells (unreife Sinushistiocytose of Lennert (12)) were usually found as well as paracortically located large lymphoid cells (immunoblasts) Giant cells of Langhans type large granulomata necrosis and fibrosis were rarely found Quite typically inflammatory infiltrate with lymphocytes and groups of epithelioid cells permeated the capsule The parasite itself was not seen for certain

Follow up The symptoms had usually disappeared by the last visit to the doctor about two weeks after the biopsy In addition the patients

Table IV Relative proportion of lymphocytes in the differential count of blood leucocytes (range 0–1 0)

	Toxoplasmosis (%) (n=77)	Non specific hyperplasia (%) (n=27)
0 30 or less	4	22
0 31–0 40	12	34
0 41–0 50	47	19
0 51–0 60	23	11
0 61–0 70	13	7
0 71 or more	1	7



Fig. 2. Histology ... case of lymph n... plasmosis. In the ... corner there are ... centers with sma... epithelioid ce... surrounding them ... of monocytoid c... top. Hematoxyla... original magn fa...

were followed on the basis of later hospital records due to other diseases. 89 patients were followed for 1–16 years (average 4.9). All the patients were checked from the Population Registry and 235 were alive. The two deaths were not related to lymph node diseases or toxoplasmosis. No later cases of malignant lymphomas were found from the Finnish Cancer Registry (total follow up 1 111 person years

Table V. *Various histological features in the 237 proved cases of lymph node toxoplasmosis*

	N	%
General structure		
Well preserved	235	99
Slightly distorted	2	1
Germinal centers		
Abundant	234	99
Sparse	3	1
Paracortical area well developed	236	100
Epithelioid cells in groups		
In the paracortical area	237	100
In germinal centers	218	92
Strands of monocytoid cells	205	87
Perinoditis	198	84
Langhans giant cells	8	3
Necrosis	5	2

191 cases excluding the most recent ones ... five years and ten months)

DISCUSSION

Toxoplasmosis comprises 5–15% of all ly... enlargements on the basis of various ma... 22, 23). In our material of excised lymph n... percentage was 2–4. In an unselected ma... bodies have been found in 15–25% of the p... in Finland (7). Toxoplasmosis can thus ... sidered a common infection, although not ... recognized.

Lymph node toxoplasmosis may manifest ... as enlarged lymph nodes, as shown by ... material collected among biopsied cases ... series of Tenhunen (21) and Rafaty (15) the ... tions of symptomatic patients were 60 ... respectively. In Tenhunen's study the ass... of the symptoms was, however, based on a ... questionnaire to the patients, and the ... were invariably mild.

Clinical diagnosis can be aided by the fa... the majority of patients with lymph node t... mosis are women, the nodes are located in ... and neck region and the duration of the ly... enlargements is often less than one month. T...

gic abnormality is quite constant relative
tosis In contrast patients with non
lymph node hyperplasia have a longer his
and relative lymphocytosis is less common
mononucleosis shares many features
oxoplasmosis as previously noted by Lennert
Patients with Hodgkin s disease usually have
general symptoms including weight loss
mia Blood tests before therapy often
leucocytosis with granulocytosis and lym
(13) The clinical features in toxoplas
are not specific however and to obtain a
an enlarged lymph node is excised
logical features in lymph node toxoplas
rather specific judging from this material
303 cases with typical histology 237 had
antibody titres The specificity of the his
l picture is thus about 80% or even higher
in many cases serological examination was
y performed before the rise of titers (19) The
correlation between the histological pic
l high toxoplasma titers has been shown by
l authors (4 14 20 24) The sensitivity of the
al diagnosis is also high because only 7
% seropositive cases in this study presented
a specific histology The histological differ
diagnosis will be treated in a forthcoming
ion

final diagnosis is made on the basis of
cal investigations For differential diagnos
ons and possible therapeutic implications
t diagnosis is needed When negative in the
rement the antibody titers should be
repeatedly The parasite can be isolated
t this is not always possible and was not
in the present cases Specific treatment is
y not required in lymph node toxoplasmosis
reserved for the most symptomatic cases
Previous lymph node toxoplasmosis does not
etal damage but infection during pregnancy
hazardous to the fetus (3 25) The source of
lasmosis cannot be determined on the basis of
material Epidemiological studies have re
a significantly higher percentage of patients
consumers of raw meat than among controls
One epidemic of five patients was probably
to contaminated hamburgers (10) Recently the
ation of Toxoplasma trofozoites through oral
membrane has been demonstrated experi
ally in the rabbit (16) This could also explain
mainly cervical location of lymph node toxo-
plasmosis Cats have formerly been considered a source of toxoplasmosis and also epidemics have recently been reported (27)

The follow up of the present cases based on the Cancer Registry data suggests that toxoplasmosis bears no relationship to malignant lymphomas the relationship observed by Sheagren et al (21) must have been co-incidental The Cancer Registry has previously on the basis of check ups proved reliable when tracing malignancies (26) The life expectancy of the patients does not differ from that of the general population

Toxoplasmosis should be considered in the clinical differential diagnosis of lymph node enlargements especially in young and female patients with cervical adenopathy and relative lymphocytosis in the peripheral blood

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REFERENCES

1 Beverley J K A & Beattie C P Glandular toxoplasmosis A survey of 30 cases Lancet 2 7043 1958
2 *Carey R M Kimball A C* Armstrong D & Liebermann P H Toxoplasmosis Clinical experiences in a cancer hospital Am J Med 54 30 1973
3 Desmonts G & Couvreur J Congenital toxoplasmosis A prospective study of 378 pregnancies N *Engl J Med 290 1110 1974*
4 Dorfman R F & Remington J S Value of lymph node biopsy in the diagnosis of acute acquired toxoplasmosis N Engl J Med 289 878 1973
5 Feldman H A Toxoplasmosis N Engl J Med *279 1431 1968*
6 Gard S & Magnusson J H *A glandular form of* toxoplasmosis in connection with pregnancy Acta Med Scand 141 59 1951
7 Gronroos P Studies on toxoplasma and the serology of toxoplasmosis Dissertation Helsinki 1956
8 *Gronroos P Ollila, O & Saxen E* Glandular toxoplasmosis A case report Ann Med Exp Fenn 33 204 1955
9 Gutesohn N & Cole P Epidemiology of Hodgkin s disease in the young Int J Cancer 19 595 1977
10 *Kean B H Kimball A C* & Christenson W N An epidemic of acute toxoplasmosis JAMA 08 1002 1969
11 Krick J A & Remington J S Toxoplasmosis in the adult—an overview N Engl J Med 298 550 1978
12 Lennert K Lymphknoten Diagnostik in Schnitt und Ausstrich Band I A Cytologie und *Lymphadenitis* Springer Verlag Berlin Gottingen and Heidelberg 1961

13 Levinson B A clinical study in Hodgkin s disease Arch Intern Med 99 519 1975
14 Piringer Kuchinka, A Martin I & Thalhammer O Uber die vorzuglich cervico-nuchale Lymphadenitis mit kleinherdiger Epitheloidzellwucherung Virchows Arch Path Anat 331 552 1958
15 Rafaty F M Cervical adenopathy secondary to toxoplasmosis Arch Otolaryngol 103 547 1977
16 Raisanen S Transmission of toxoplasmosis with trophozoites An experimental study Acta Universitatis Tamperensis Ser A 84 1977
17 Remington J S Toxoplasmosis in the adult Bull NY Acad Med 50 211 1974
18 Saxen E & Saxen L The histological diagnosis of glandular toxoplasmosis Lab Invest 8 386 1959
19 Saxén E Saxen L & Gronroos P Glandular toxoplasmosis A report of 23 histologically diagnosed cases Acta Pathol Microbiol Scand 44 319 1958
20 Saxen L Saxen E & Tenhunen A The significance of histological diagnosis in glandular toxoplasmosis Acta Pathol Microbiol Scand 56 284 1962
21 Sheagren J N Lunde M N & [illegible] Chronic lymphadenopathic [illegible] 60 300 1976
22 Siim J Chr Toxoplasmosis acquisita lymphonodosa clinical and pathological aspects [illegible] Sci 64 185 1956
23 — Toxoplasmosis WHO Tech Rep Ser 431 [illegible]
24 Stansfield A G The histological diagnosis of [illegible]plasmic lymphadenitis J Clin Pathol 14 565 [illegible]
25 Tenhunen A Glandular toxoplasmosis [illegible] of the disease in Finland Acta Pathol Mi[illegible] Scand (Suppl) 172 1964
26 Teppo L Hakama M Hakulinen T Le[illegible] M & Saxen E Cancer in Finland 1953-1970 [illegible]dence mortality prevalence Acta Pathol Mi[illegible] Scand (A) (Suppl) 252 1975
27 Teutsch S M Juranek D D [illegible] P & Sikes R K Epidemic [illegible] sociated with infected cats N Engl J M[illegible] 1979

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Angiotensin Converting Enzyme in Newly Detected Sarcoidosis

With Special Reference to Enzyme Levels in Patients with Erythema Nodosum

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ABSTRACT Serum angiotensin converting enzyme (SACE) was measured in 56 patients with sarcoidosis within three months after diagnosis Serial analyses were performed in 42 patients who were followed for 3 months to one year SACE was elevated in 49 (%) of the patients at some time during the period of observation Erythema nodosum (EN) was present in 14 patients Only one out of seven had elevated SACE during EN but four months later SACE was elevated in all 14 In this group there was a negative correlation between SACE and S lysozyme Among patients without EN the frequency of SACE elevation was rather constant, about 60% In half of the patients SACE was normal at first examination and subsequent elevation was observed in 19% SACE and S-lysozyme were positively correlated Enzyme activity was independent of mode of presentation but a significant trend toward higher SACE in patients with pulmonary involvement was observed Changes in SACE were roughly correlated to roentgenological changes Among healthy controls significantly higher SACE levels were found in children up to 17 years of age (reference interval 21.2– U/ml) than in adults aged 18–65 years (12 0–36 8 U/ml) The observations on patients with sarcoidosis demonstrate that a unique pattern of SACE occurs in patients with EN different from that of patients without EN The findings support the view that EN is a hallmark of acute-onset sarcoidosis The value of serial SACE analyses is emphasized

Key words angiotensin converting enzyme lysozyme sarcoidosis erythema nodosum age variation

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Since the first extensive study on serum angiotensin converting enzyme (SACE) in sarcoidosis (9) elevated enzyme levels in patients with this disease have been noted by several investigators with a frequency ranging from 29 (25) to 88% (9) This range is independent of method and may be due to the composition of series with different proportions of active and inactive cases

Among cases of newly detected sarcoidosis (i e subacute) elevated SACE has been found in 45 60% (23 24 25) but the figures are difficult to interpret because examination occurred at different times in the course of disease

The aim of the present study was to examine SACE in newly detected sarcoidosis with special reference to clinical mode of presentation Furthermore a reference group of children is presented

SUBJECTS

The series consisted of 56 consecutive patients with newly detected sarcoidosis during a two-year period in 1977 79

The diagnosis of sarcoidosis was made without knowledge of the SACE level and was stated according to clinical and roentgenological criteria (18 20) Non caseating epithelioid granulomas were found in 21 patients Haematological bacteriological and serological investigations were performed in all patients in order to exclude the possibility of tuberculosis yersiniosis other infectious diseases and malignant disorders In 54 patients the first SACE analysis was performed within two months after the diagnosis of sarcoidosis and in two patients after three months

The patients were divided into two groups according to presence or absence of erythema nodosum (EN) (Table I) Only one SACE analysis was performed in 14 patients (among them one with EN) 2 12 analyses were performed in 42 The follow up time was 2 months to 1 year (mean 9 months)

In the following time 0 indicates the onset of EN in patients in whom a distinct debut could be assured as regards patients without EN it indicates the point of time when the first signs of sarcoidosis appeared i e first abnormal chest X ray (CXR) suggesting the disease

As adult controls we used 116 healthy persons aged

Abbreviations ACE angiotensin-converting enzyme SACE serum ACE CXR = chest X-ray EN = erythema nodosum

Table I *Sex and age distribution of the 56 patients*

	N	%	Males	Females	Age (y)	
					Mean	Range
With EN	14	25	7	7	28	19–58
Without EN	42	75	25	17	31	16–66
Total	56	100	32	24	30	16–66

18–65 years (14) In view of recent reports on age variation of SACE (13) 86 non sarcoid children aged 5 months – 17 years were examined (17) The male female ratio was 40 46

METHOD

SACE was analysed according to Cushman and Cheung (1) as modified by Lieberman (9) SACE activity was expressed in U/ml equivalent to nmoles of hippuric acid liberated per ml per min

Serum lysozyme was determined immunochemically according to the method of Laurell (Medicinsk Laboratorium Copenhagen) Reference interval 0 08–0 32 μmole/l

The cumulated frequency of elevated SACE was calculated in the following way

$$\frac{\text{No of pats with elevated SACE during a given period} \times 100}{\text{Total no of pats examined during the same period}} \%$$

For example at time 0 months 14 out of 20 patients examined had elevated SACE = 70% At 1 month 5/16 had elevated SACE = 31% At this time a total of 32 patients had been examined 16 of these 32 had elevated SACE giving a cumulated frequency of 16/32=50% At 2 months elevated SACE had been found in 20 out of 39 patients examined during time 0–2 months giving a cumulated frequency of 51% etc

Statistics (4)

Differences between mean values were calculated using Student s t test in small subgroups using the Mann Whitney rank sum test Difference of frequency was calculated with χ^2 test and correlation with Spearman s rho Significance level 5%

RESULTS

Controls

Fig 1 shows a significant difference ($p<0$ 01) between SACE in persons up to 17 years of age (SACE 32 2±5 5 U/ml (mean ±1 S D)) and adults aged 18–65 years (SACE 24 4±6 2 U/ml) Thus the reference interval (mean ± 2 S D) was 21 2–42 2 and 12 0–36 8 U/ml respectively Fifteen (17%) of the children had SACE above the upper limit for adults No sex difference was noted

Sarcoidosis patients as a whole

Considering all 56 patients elevation of SACE observed in 15 (56%) out of 27 at time 0 And 39 patients (70%) had elevated SACE when served for up to one year Among 21 patients whom non caseating epithelioid granulomas detected elevated SACE occurred in 14 mean SACE 45 5 U/ml Among 35 patients no tissue biopsy was performed the corresponding figures were 21 (60%) and 47 4 U/ml The difference was not significant No relationship was found between SACE and systemic blood pressure

Sarcoidosis without erythema nodosum

Among the 42 patients without EN 31 (95%)

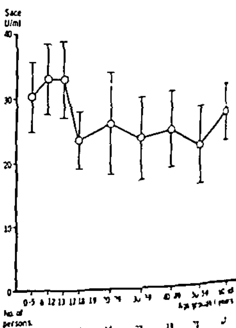


Fig 1 SACE levels of the control subjects show decrease in persons over 18 years of age compared with those 17 years of age or younger

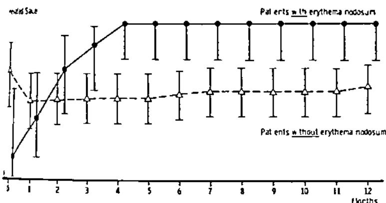


Fig 2 Cumulated frequency of elevated SACE including 95% confidence limits in patients with and without EN

...ted SACE (mean 41 4±16 4 U/ml) at first ...ination at 0–3 months which is significantly ... than in the controls ($p<0$ 001) Twenty pa... were examined at time 0 14 (70%) of these ...levated SACE

...ur (19%) of 21 patients with normal SACE at ...examination developed an elevated enzyme ...during the time of observation giving a total ...ency of SACE elevation of 25/42=60% (95% ...dence limits 43 3–74 4) as demonstrated in ... Mean SACE in these patients displayed fluc...ons with no consistent pattern

...ong the patients with a persistently normal ...E at serial analyses deviations of more than ... were noted in five two with increasing and ... with decreasing SACE

...e highest SACE observed was 116 1 U/ml ...maximal SACE was 44 2±20 0 U/ml

...enty three patients were admitted because of ...toms of disease and 19 were detected on ...ne CXR The frequency of SACE elevation at ...examination was the same in both groups 52 ...17% respectively

As shown in Table II a trend towards a higher mean SACE and a higher frequency of elevated SACE was found in patients with CXR stages II+III (only one patient had stage III) than in patients with CXR stage I but the difference was not significant

The course of the disease in relation to SACE levels is demonstrated in Table III No consistent pattern could be found But among 30 patients with a regular CXR follow up regression was noted in 12 (40%)—in three patients in spite of increasing SACE Only one patient showed progressive lung changes

Serum lysozyme was analysed in 20 patients Fig 3 demonstrates a positive correlation between SACE and serum lysozyme ($p<0$ 001) Among 33 paired values an elevated serum lysozyme despite a normal SACE was noted in 11 (33%) whereas both SACE and serum lysozyme were elevated in 19 (58%) In no instance was there elevated SACE despite a normal serum lysozyme

Among patients with normal SACE at first examination 12/19=63% were tuberculin negative

...e II *S angiotensin converting enzyme (mean ± S D) related to chest X ray in 42 patients with ...oidosis without erythema nodosum*

...	No of pats	SACE at first examination U/ml	Pats with elevated SACE n	Pats with elevated SACE %	Maximal SACE (U/ml)	Total frequency of elevated SACE n	Total frequency of elevated SACE %
I	20	38 0±14 3	9	45	43 2±20 5	11	55
II	22	42 9±18 1	12	55	45 0±17 9	14	64
...	42	41 4±16 4	21	50	44 2±20 0	25	60

Table III *Relationship between S angiotensin converting enzyme and chest roentgenographic c... 42 patients with newly detected sarcoidosis observation period 2–12 months*

Course of SACE	Course of CXR changes			
	Progression	No change	Regression	Total
Pats with EN (n=14)				
(only a single analysis performed in 1 pat)				
Increase	4	5	3	12
No change	0	0	0	0
Decrease	0	0	1	1
Total	4	5	4	13
Pats without EN (n=42)				
(only a single analysis performed in 12 pat)				
Increase	1	8	3	12
No change	0	3	2	5
Decrease	0	6	7	13
Total	1	17	12	30

compared with 13/16=81% among patients with elevated SACE This difference was not significant

Sarcoidosis with erythema nodosum

EN was the first sign of sarcoidosis in 14 patients in eight cases preceded by arthralgia or arthritis for days to weeks SACE was examined during EN (time 0) in seven of these patients After one month SACE had been analysed in 13 patients and after two months in all 14

Fig 2 shows that only one (14%) out of seven patients examined during EN had an elevated SACE while it increased gradually in 13 during the following weeks to months in one patient as late as after four months at which time SACE had been elevated in all patients This frequency of SACE elevation was significantly different from that noted in patients without EN as estimated by confidence limits (14/14=100% 95% confidence limits 76 8–100) Mean SACE is shown in Fig 4 where a continuously normal SACE in three patients with non sarcoid EN is shown for comparison

In one patient only a single analysis was done Significant changes in SACE occurred in all others as a rule an increase This course was in contrast to that of patients without EN In the patient with elevated SACE at time 0 SACE began to decline after four months simultaneously with regression of pulmonary infiltrations

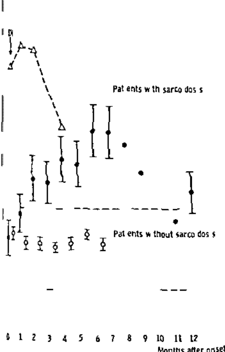
There was no relationship between the stage of CXR and SACE (10 patients had stage I and 4 stage II) The relationship between the course ... and SACE levels is shown in Table III A... increasing SACE was not followed by a ... pattern of changes in CXR it should be no... the only patient with a decreasing SACE ... comitant roentgenological regression

Maximal SACE was 53 9±12 8 U ml ... significantly higher than the correspond... for patients without EN ($p<0.05$)

In contrast to patients without EN a...



Fig 3 Correlation between 33 correspon... serum lysozyme and SACE in 20 patients w... Rho = 0 702 $p<0.001$



/ SACE (mean ± S D) in 13 patients with sar and EN SACE of an additional patient with 4 SACE during EN is showed separately For SACE in three pat ents with non sarcoid EN cated

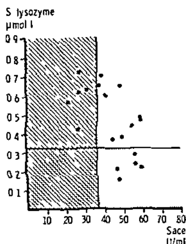


Fig 5 Correlation between 19 corresponding values of serum lysozyme and SACE in 6 patients with sarco dosis and EN Rho = −0 512 $p<0\ 05$

between SACE and serum lysozyme bserved in patients with EN ($p<0\ 001$) (Fig rum lysozyme was uniformly elevated during n all patients examined and decreased subly while SACE increased typically for to months after EN The course of a reptative patient is shown in Fig 6

13 patients 12 (92%) were tuberculin nega and no relationship was found between SACE uberculin reactivity

DISCUSSION

Lofgren s classical study on subacute sar sis (11) it has been realized that sarcoidosis EN in many ways behaves in a special manner ng a most favourable prognosis and particu mmunological features e g a relatively high ncy of circulating immune complexes (7) e cases are also unique because the onset of dosis can be established with relative certain 0)

The present study presents another characteristic feature of sarcoidosis with EN i e these patients have usually a normal SACE at the onset of EN —despite concomitant presence of epithelioid granulomas and tuberculin negativity—followed by a distinctly increasing SACE This finding is in contrast to the situation in patients without EN who have a relatively stable frequency of SACE elevation (60%) and supports the concept that EN is in fact an expression of the onset of sarcoidosis It was also remarkable that serum lysozyme was elevated during EN in all sarcoidosis patients examined with a subsequent decline and a negative correlation to SACE—in contrast to patients without EN This phenomenon may be a clinical correlate to the experimental findings of Lieberman et al (10) They induced lung granulomatosis in rabbits with a complete Freund s adjuvant and noted an increasing SACE after three weeks On the other hand serum lysozyme was elevated after only two days with a peak after three weeks

The total frequency of elevated SACE of 70% in newly detected sarcoidosis is higher than that of 49% reported earlier (14) The cause of this seeming discrepancy is in part that serial analyses will unveil a larger number of enzyme elevations Another reason is that patients with subacute sarcoidosis in our previous study had a duration of disease up to two years at the time of blood sampling In some of these patients therefore a previous SACE elevation may have occurred before

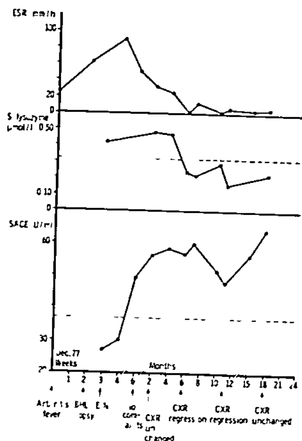


Fig 6 Course of SACE serum lysozyme ESR and clinical signs in a 31 year-old male with sarcoidosis presenting with arthritis and EN BHL = bilateral hilar lymph adenopathy

examination However in spite of serial analyses the frequency of enzyme elevation in most of the patients in the present series was not as high as the 85% reported in patients with an active disease of more than two years duration (14)

Even if a patient s SACE is within the normal limits at several examinations a rise or fall within these limits may occur suggesting disease activity Such fluctuations were observed in five patients with sarcoidosis whereas similar analysis in normal persons showed a stable SACE for weeks and months

Other investigators have found that SACE is higher in patients with roentgenological lung involvement than in patients with CXR stage I (6) Although the present series shows a trend against this the difference is not significant In fact CXR gives only a rough impression of pulmonary involvement Thus Rosen et al (19) found lung granulomas in all of their 21 patients with CXR stage I (isolated hilar or paratracheal adenopathy without pulmonary infiltrations) This ob[illegible] is in accordance with the view that sa[illegible] —even when the only manifes[illegible] adenopathy—is a multisystem disorder demonstrated by the relatively high freq[illegible] clinically inert sarcoidosis of the spleen liver (8)

The clinical course of sarcoidosis d[illegible] period of observation was roughly correl[illegible] levels of SACE Progressive intrathorac[illegible] associated with decrease in SACE were [illegible] served but roentgenological regression wa[illegible] six patients despite increasing SACE

The cause of SACE elevation in sa[illegible] still unknown although experimental a[illegible] observations point to the mononuclear ma[illegible] cell line as a primary source of SACE in th[illegible] (3 10 22) In addition to blood and ep[illegible] cell granulomas increased ACE has [illegible] been demonstrated in alveolar macrophag[illegible] patients with sarcoidosis (3) Although S[illegible] sarcoidosis is useful in diagnosis and mo[illegible] the disease the pathophysiological sig[illegible] unclear Thus no correlation has been fo[illegible] tween systemic blood pressure and SACE [illegible] other series (9) neither has a correlation be[illegible] between plasma renin activity and a[illegible] sarcoidosis (26) Involvement of the re[illegible] giotensin system in sarcoidosis is theref[illegible] ly However the other physiological r[illegible] enzyme is bradykinin degradation (kinina[illegible] and perhaps the elevated SACE in sarco[illegible] flects an involvement of kinin metabolism [illegible] disease has the character of a chronic infla[illegible] The different course of serum lysozyme and S[illegible] in patients with EN suggests that lysozyme [illegible] ACE are produced from different cell [illegible] more probably from different stages in the [illegible] ment of epithelioid cells Another obs[illegible] is the age variation of SACE in no[illegible] persons—with a higher level in children a[illegible] agers This finding is in agreement w[illegible] publications (5 13)

It has been stated that other ACE assays [illegible] other substrates or by spectrofluorometry [illegible] 24) should be more convenient and spe[illegible] the present one However with respect to [illegible] sarcoidosis the frequency of enzyme eleva[illegible] the same magnitude in most series indepen[illegible] method Furthermore the present assay has a[illegible] hands been very precise with a coefficient of va[illegible]

f 0 03–0 0› (15) The elevat on of enzyme eems to be rather spec f c for sarco dosis f l e pos t ve rates ranging from 0 8 (14) to 4) A recent survey from our laboratory (16) ved elevated SACE in only about 1% of 778 s and non sarcoid patients exam ned

ACKNOWLEDGEMENT

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REFERENCES

u hman D W & Cheung H S Spectrophotomet c as ay and propert es of the angiotens n convert ng me of rabb t lung B ochem Pharmacol 0 1637 1971

riedland J & S l erste n E Fluorimetric assay for angiotens n-convert ng enzyme w th the natu d subs rate ang otens n I Am J Cl n Pa hol 68 2_5

J L Bodel P T H nman L M Stevens C Matthay R A & Reynolds H Y Mononuclear ytes in sarco dos s Lysozyme and angiotens n converting enzyme In VIIIth Internat onal Con ence on Sarco dos s and Other Granulomatous ases (ed W J Williams & B H Dav es) p 417 a Omega Publ sh ng Ltd Cardiff Wales UK 80

Sc entif c Tables 7th ed Basel Sw tzerland 70

onhagen R ska C Ang otens n-convert ng en e I Act v ty and correlat on w th serum ozyme in sarco dos s other chest d seases or mph node d seases and healthy persons Scand J r D s 60 83 1979

onhagen R ska C Selroos O Wagar G & hrqu st F Ang otensin con ert ng enzyme II um activ ty n early and newly detected sar s Scand J Re p r D s 60 94 1979

nes J V C rculat ng mmune complexes n hema nodosum and early sarco do s Lancet 153 1976

ehmuskall o E Hannuksela M & Halme H The er n sarco dos s Acta Med Scand 0 89 1977

eberman J Elevat on of serum ang otens n-con erting enzyme (ACE) level n sarco dos s Am J Med 59 365 1975

ieberman J Kanesh ro W Sastre Foken A Messer K & Rea T Serum ang oten n-con ert ng nzyme and lysozyme n rabb ts w th pulmonary lomatos s nduced by complete Freund s adju ant and B C G In VIIIth Internat onal Conference on Sarco dos s and Other Granulomatous D seases (ed W J W ll ams & B H Dav es) p 111 Alpha Omega Publish ng Ltd Card ff Wales UK 1980

11 Lofgren S Primary pulmonary sarco dosis II Cl n cal course and prognosis Acta Med Scand 45 465 1953

12 Rohatg P K Massey T H & Ryan J W Serum ang otens n convert ng enzyme and sarco do s Cl n Res 6 6?A 1978

13 Rohrbach M S & DeRemee R A Serum ang oten s n convert ng enzyme activ ty in sarco dosis as measured by a s mple rad ochem cal assay Am Rev Resp r D s 119 61 1979

14 Rømer F K Angiotensin convert ng enzyme n sar co dos s Acta Med Scand 06 7 1979

15 — Ang otens n konverterende enzym som d agnos t kum ved nyopdaget sarko dose sammenl gnet med lungecancer og tuberkulose Ugeskr Laeger 14? 806 1980

16 Rømer F K & Emmertsen K Serum ang otens n convert ng enzyme in sarco dos s Hodgk n s d sease and mal gnant blood d seases Proc Internat onal S e na Sarco dos s Sympos um S ena Italy Sept 1979 In p ess 1980

17 Rømer F K Ibsen K K Friis B & Koch C Serum ang otens n convert ng enzyme activ ty in chron c granulomatous d sease Lancet ? 860 1979

18 Rømer F K Paulsen S Anton us V N elsen J L & Hommelgaard P Sarco dos s n a Dan sh amt A retro pective ep dem ological study of sar co dosis n Ringkøb ng amt from 1960 to 1969 Dan Med Bull 0 11? 1973

19 Rosen Y Amorosa, J K Moon S Cohen J & Lyons H A Occurrence of lung granulomas in pa t ents w th stage I sarco dos s Am J Roentgenol 1?9 1083 1977

20 Scadd ng J G Sarco dos s Eyre & Spott swoode London 1967

21 Selroos O Sarco dos s of the spleen Acta Med Scand 00 337 19 6

22 S l erste n E Friedland J & Ackerman T Eleva t on of granulomatous lymph node and serum lysozyme n sarco dos s and correlat on w th an g otens n con ert ng enzyme Am J Clin Res 68 ?19 1977

23 S l erste n E Friedland J K tt M & Lyons H A Increa ed serum ang otens n con ert ng enzyme act v ty n sarco dos s Isr J Med Sc 13 995 1977

24 Studdy P B rd R James D G & Sherlock S Serum ang otens n-convert ng enzyme (SACE) n sar co dos s and other granulomatous d sorders Lancet 1331 1978

25 Turton C W G Grundy E F rth G M tchell D R gden B G & Turner Warw ck M Value of measuring serum ang otens n I con ert ng enzyme and serum lysozyme n the management of sar co dos s Thorax 34 57 1979

26 Wilton A Da ies B H & W lliams W Plasma ren n act v ty and ang otens n II concentrat ons n sar co dos s Br Med J IV 1 6 1977

A u

Prodromal Ventricular Premature Beats Preceded by a Diastolic Wave

Gunnar Ejv nsson and Erik Or nius

From tl e D s ns f C rd olog Depart e ts of Med c e Hudd nge Hosp tal d Karol ska H sp tal St ckl ol S ede

TRACT In a prospective study of quinidine syn 71 patients with atrial fibrillation/flutter were monitored for four days after the start of d ne therapy Six patients developed ventricular card a (VT) or ventricular fibrillation (VF) dur he first 48 hours in sinus rhythm Q–T prolonga as seen in most patients with and without VT/ d was non predictive in this respect However stolic wave (DW) of larger amplitude than the eding T wave and usually followed by a ventricu remature beat (VPB) appeared in five of the six F pat ents (13–185 min before the first event) n none of the remaining 63 patients reaching rhythm For comparison two of our own cases ane from the literature with idiopathic long Q–T ternating T wave syndromes were studied for DW–VPBs They were found in all ten cases a VPB recording but among 19 patients with myocardial infarction and VT/VF no such case een As VT/VF was more common after large VPB after small amplitude DWs it is discussed her the DW not only precedes but also initiates ntricular tachyarrhythmias

o ds qu n d ne syncope long Q T syndrome al er T wave syndrome

Med Scand 208 445 1980

a well known paradox that quin dine although etimes used to prevent ventricular tachyar hm as in other cases may produce ventricular h card a (VT) or ventricular fibr llat on (VF) It been suggested that these qu n d ne nduced yarrhythm as represent a form of the Q T pro at on syndrome and that the Q–T nterval uld be mon tored n pat ents receiv ng qu n d ne A retrospect ve study showed however that prolongat on is an unspec f c pred ctor of these VFs (5)

he a m therefore was to study in a prospect ve es all ECG changes preced ng VT and VF by cont nuous monitoring dur ng the f rst days of qu n d ne therapy Pat ents with id opath c long Q–T syndrome (24) and the related alternating T wave syndrome (18 21) were also stud ed for com parison as were patients with acute myocard al in farct on (AMI) and VT/VF

PATIENTS AND METHODS

Q d ne VT/VF

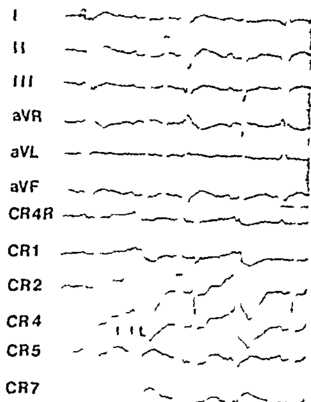
Th s prospect e study (1976–78) comp sed 72 pat ents 25 females and 47 males aged 33 8? years (mean 61) They were hosp tal zed for convers on of atr al f brillat on (64) or flutter (8) The et ology was apparent n only 9 cases valvular heart d sea e 9 ischem c heart d sease 6 system c hypertens on 5 treated thyrotox cos s 4 al cohol sm 3 cor pulmonale ?

All pat ents had been treated w th d gox n but n 60 cases th s was w hd awn 2 14 days before the con ers on attempt Qu n d ne sulphate was g ven perorally in a load ing dose of 0 01 g/kg b wt and a ma ntenance dose of 0 6 g (durules) started one hour later every 1 th hour One pat ent developed an allerg c react on after the load ng dose and was excluded from the ser es

Th rty four pat ents con erted to s nus hythm w th n 15 hours after the f rst dose of qu n d ne after that n er val 35 of the rema n ng 37 pat ents were DC-converted to s nus rhythm by max mally 75 300 Wsec (mean 169)

All pat ents were ECG mon tored for 94 hou s from the start of qu n d ne therapy by a rhythm lead correspond ng to CR 1 Th s cable ECG was also recorded cont nuously at a paper speed of 10 mm/sec by an ink jet recorder The record ngs were evaluable for 95% of the t me A 12 lead ECG was recorded tw ce da ly du ng these four days The Q T nterval was measured as the mean of two cycles n lead II of the 12 lead ECG reco ded about 24 hours after the start of qu n d ne treatment The meas- u ement was performed only n the 34 pat ents in whom both observers cons dered the Q T end po nt d st nct The upper normal l m t was accord ng to Lepeschk n (16)

Abbre at ns VT = vent cular tachycardia VF ven tricular f br llat on VPB = ventricular premature beat DW = d astol c wave AMI = acute myocard al nfarct on



F g 1 A 12 lead ECG from a pat ent w th qu n d ne nduced VF how ng a diastol c wave (between the first two arrows) pre ed ng a VEB One large square represents 0 1 sec and 0 5 mV

Id pati l ng Q T s ndr e

Th s group ncluded the only pat ent w th d opath c long Q T syndr me n our files and e ght cases found n the literature w th a good record ng of the tachyarrhythm a (7 9 11 12 17 0 23)

Our pat ent was a 43 year-old man w th a h story of many ep sodes of d zz ne s and palp tat ons espec ally when runn ng uph ll and dur ng emot nal stress He had also had two syncopes and on these adm ss ons the ECG showed VT wh ch was not of t sade de po ntes type The Q–T nterval was prolonged dur ng per ods of ven tricular ect pi beats but n t therw se For seven years n w he has been almost completely free from attacks of d zz ness on β block ng therapy

Al e nat n T wa e nd me

Th s group n ludes the only pat ent w h alternat ng T wave and VT/VF in our files and the nly case found in the l terature w th a record ng of the tachyarrhythm a (1)

Our patient was a 19-years-ld w man w th a sl ght d gox n ntox ation (3 3 nmol/l serum when she needed an acute operation w th a valve pros he s because of septic aortic incompetence (19) On the day of peration she developed VF on the next day a long VT f torsade de po ntes type was recorded The Q–T nterval was pro-

longed during the first post pera e (a) Th not have any h story f sn ope and had not w th any drug known to affect the Q–T ıe

Ac te n ard I nfarct n

For comparison rhythm strips f m 19 AMI VT/VF were stud ed N ne were conse c mpl cat ng but not agonal VF cases and t ents w th VT d agn ed by fusi n beats

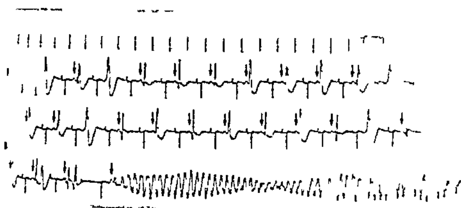
RESULTS

Q l VT/VF

Of the 71 p ti ents four devel ped VF on one or m re occasions dur ng the tw in s nus rhythm When long enough to be the VTs were often (63) f to sade type No pat ent was known to have h before There was no d fference betwee with and without VT/VF with regard to s centrat ons f potass um treat n ne q digoxin and even the nteraction nate oxin concentrati n fo llow ng qu n d re in the two gr ups (4)

In 34 of the 71 p tients the T wa e had end point so that the Q–T interval c uld ured In 87% of them the Q–T nterval longed includ ng all five measurable V tients and the five were scattered others e the specificity of Q T prolong pred ctor of VT/VF was very low An in the ECG showed a good pred t ty f a d ast l c wave (DW) f greater amp the preced ng T wave (F g 1) which exceptions w s followed by a ven r ture beat (VEB) The DWs occurred n f patients with VT VF and in none f reach ng s nus rhythm After 3–47 unc in s nus rhythm the DWs f rst appeared (mean 55) before the f rst ep s de f VT same time as the DWs frequent VEBs usually in a b gem ny pattern

In Fig 1 the DW follows every s be best seen in leads CR_2 and CR betwe two arrows The ampl tude increases from the f rst arrow unt l a prematu e be broad QRS complex arises at the se The third arrow den tes where the next would have started and it is appa t st ll has a large ampl tude l e in cases in F 1 cannot be the in tial part f QRS complex as that would mean a QRS



A rhy hm strip (correspond ng to lead CR ₂) ɪ g dias olic wa es (arrows) followed by VPBs and by VT of torsade de po ntes type n a pat ent on

qu n d ne The reco d n ont n One large repre ents 0 5 sec

e 0 3 sec wh ch s not resonable Nor is it a ure P wave superimposed on the T-U wave R) as the P duration would then be about sec The DW ought not to be called a g ant U as hat term has been used for moderately U wa es n e g hypokalem a wh le th s DW arger ampl tude than the T wave of the same

g 2 shows how w de premature QRS preceded DV starts after a long R R interval caused by a ure P The b gem ny goes on for about 1 min t turns into VT of torsade de po ntes type er on VF

3 shows that DWs of small ampl tudes are d by s ngle premature beats or couplets and of la ge ampl tudes by VTs This seems also the case n Fig 2 although less marked In her of the five pat ents the phenomenon was as n t as n Fig 3

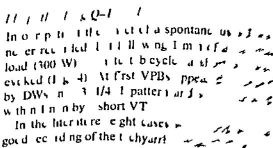
he VPBs and the first beat in VTs and VF ed vary ng conf gurat ons n each pat ent and the DW varied too There was n fixe l c t tion of DW VPB configurations

As rare except ons DWs were ı t ll ı l by VPBs Somet mes there s ı ı t ıter the DW altl o gh t ı ı t little ı configuration from the s nus be ts O ı the ı ıs the DW was not followed by ı t ı beat and that appe red to h ppen ı pecially just fter a VT or VF had stopped In these ı the DWs could show a ı ı p ttern all the ı rhythm although every sec nd DW ı ı ı rger ampl tude

ıı ı ıı ı & Q-I ı

In o r p ı ı t ı a spontane ı ne er rec ı ded ı ı ı ı w ng I m ı load (300 W) ı t ı b cycle ı evoked (Fig 4) At first VPBs ppea by DWs n 3 1/4 1 patter with n 1 n n by short VT

In the literature e ght cases good d cc rd ng of the t chyarr



3 A rhythm strip (correspond ng to lead CR ₂) show the d astol c waves arrows) of mall ampl udes are by VPBs and waves of large amp udes by VT in a pat ent

0 5 sec

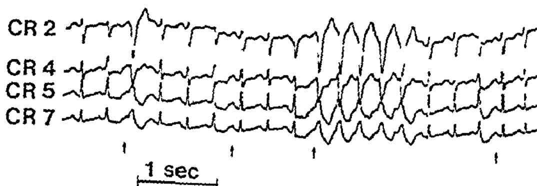


Fig. 4. Chest leads recorded 1 min post maximal bicycle exercise (300 W) for 1 min in a patient with idiopathic long Q–T syndrome. Diastolic waves (arrows) a... followed by VTB or VT and sometimes not

12, 17, 20, 23). In five cases a DW can be seen to precede the first beat of the VT/VF (7, 12, 17, 20, 23), and in three there are DWs ahead of the VPBs (2, 9, 11), as in the other four with a recorded VPB (7, 12, 17, 23).

Alternating T wave syndrome

In our case the ECG showing alternating T waves and VPBs in bigeminy or quadrigeminy (Fig. 5, top) was recorded immediately after a VT of torsade de pointes type. Both the T wave alternation and the VPBs were suppressible with lignocaine (Fig. 5, bottom) and isoprenaline (19). Fig. 5 shows, from comparison of the two panels, that the T alternation is caused by a wave superimposed from the apex of the T wave onto the P wave. When this DW has a larger amplitude, as in the first and last complex in Fig. 5, top, it precedes a VPB, but when the amplitude of the DW is smaller, as in the middle complex, no VPB follows it. The only case found in the literature showed DWs preceding both VPBs and VT (1).

Acute myocardial infarction

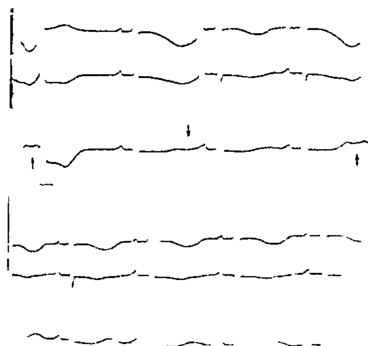
None of ten AMI patients with VT showed a DW. In one of nine AMI patients with VF it was debatable whether the second and following beats were preceded by a DW, but the first one was definitely not and there were no prodromal VPBs.

DISCUSSION

DWs followed by VPBs can also be seen in published cases of quinidine syncope (10, 13, 14, 22). This prospective series demonstrates their role as a highly sensitive (5 of 6) and specific (5... tor of VT/VF during quinidine thera... longed Q–T interval was much more co... the DWs and had a very low predic... whereas DWs followed by VPBs can be... prodromal. Their onset is early enou... phylactic measures. The impending VT... to be preventable by lidocaine pro... doses are used (150 mg as bolus+4 mg... tients below 60 years, 100 mg+3 mg... years) (5). According to the ECGs in the... and our own, DWs followed by VPBs s... prodromal also in patients with idiopathi... and alternating T wave syndromes, and... the relationship between the DWs and th... rhythmias still more interesting.

The DWs and the VPBs usually appe... neously and then occur together and dur... they disappear at the same time (19). V... usually preceded by DWs of larger am... are VPBs. For these reasons it is probab... DW not only precedes but initiates VPB... This hypothesis is not contradicted by the... a preceding DW was not seen in one of... VT/VF patients, as the monitoring lead... ideal compared to the 12 lead ECG f... DWs.

A recording published by Garza et al. (... supports further the hypothesis of a causal... ship between DWs and ventricular tach... mias. They provoked VF by epinephrine a... tion in a brain damaged patient with beta... Q–T syndrome. Studying that ECG, one... how a DW successively separates itself fr... wave and increases its amplitude until it be...



F g 5 Extrer ıy l u corded atter a V I n p w th al erna ng T ter cardıac surge S nus rhythm w I preceded by a d a (↑) When the amn the d astol c wave ı (↓) it ıs not fcllowed VPB The alternat ng ı pattern ı pparent by e panr h QRS-T m- plexe 3 and 4 *B* Th sarne l ad ı ru d 0 m a e durıng I a n t ea T T wave a a t on d a c wa es a d VIB ar no d t ta e On larg q e c en 0 I s a d mV

the R wave (lead II) and begins to be fol by VPBs and finally VF

ese findings in the surface ECG are supported cent report by Lazarra et al (15) on ventricu ar electrograms (1 cm apart) in a case of Q-T syndrome They found especially in the parts of both ventricles slow potential following the T waves These waves in d in ampl tude during infusion of epinephrine then they became high they were followed by It s not known if the surface ECG simul) showed any DWs The authors suggest abnormal afterpotentials cause both the Q-T ation and—during adrenergic stimulation— achyarrhythmias of the long Q T syndrome DW may also correspond to the second de of the r ght ventricular monophasic action described by Gavrilescu and Luca (8) eflect on was recorded in some catheter posi wo cases of congen tal long Q-T syndrome at any s te in a th rd case of the quinidine syndrome It is less clear whether the basis slow potent al waves and the DWs are the l als stud ed in isolated preparations (3 6) rong tendency of the VPBs to appear in a al rhythm gives some support for the idea

In conclus on in patiet ts n quin dine I V lowed by VPBs are a h ghly sensitive and sp pred ctor of VT/VF within the nearest m n a hours The Q-T prolongation is non pred n this sense This probably also holds true n pat ents with idiopathic long Q-T and alternating T wave syndromes

REFERENCES

1 Bashour T Rios J C & Gorman P A U wave alternans and ncreased ventricular ırrıtab l ty Chest 64 377 1973
2 van Bruggen H W Sebus J & van Heyst A N P Convulsive syncope result ng from arrhythm a in a case of congen tal deafness w th ECG abnormal t es Am Heart J 78 81 1969
3 Cranefield P F Act on potentials afterpotent als and arrhythm as C rc Res 41 415 1977
4 Ejvinsson G Effect of qu n d ne on plasma concen trat ons of d gox n Br Med J 1 279 1978
5 — K nid nsyncope p 37 Thes s Stockholm 1978
6 Ferrier G R D gital s arrhythm as role of osc lla tory afterpotent als Prog Card ovasc D s 19 459 1977
7 Garza, L A Vick R L Nora J J & McNamara D G Heritable Q-T prolongat on w thout deafness C rculat on 41 39 1970
8 Gavrilescu S & Luca C R ght ventricular mono- phas c act on potent als in pat ents w th long QT syndrome Br Heart J 40 1014 1978

9 James, T N Congenital deafness and cardiac arrhythmias. Am J Cardiol 19 627 1967
10 Jenzer H. R. & Hagemeijer F. Quinidine syncope torsade de pointes with low quinidine plasma concentration. Eur J Cardiol 4 447 1976
11 Jervell, A. & Sivertssen, E Surdo-cardial syndrom. Nord Med 76 1443 1967
12 Johansson B W & Jorming, B Hereditary prolongation of QT interval. Br Heart J 34 744 1972
13 Kaplinski E Yahini J H. Barzilai, J & Neufeld H N Quinidine syncope report of a case successfully treated with lidocaine Chest 62 764 1972
14 Koster R W & Wellens, H J J Quinidine induced ventricular flutter and fibrillation without digitalis therapy Am J Cardiol 38 519 1976
15 Lazzara R. Hope R. R. Freeman, C C & Scherlag E Afterpotentials as a cause of long QT syndrome?—Electrophysiological studies of a case Am J Cardiol 45 472 1980
16 Lepeschkin E Das Elektrokardiogram Fig. 54 Steinkopff Dresden 1957
17 Mullican Jr W S & Fisch, C Postextrasystolic alternans of the U wave due to hypokalemia. Am Heart J 68 383 1964
18 Navarro-Lopez, F Cinca J Sanz G [illegible] Magrina J & Betriu A. [illegible] Am Heart J 95 [illegible] 1978
19 Orinius E. [illegible] wave [illegible] tachyarrhythmias and [illegible] isoprenaline Acta Med Scand 2[illegible]6 [illegible] 197[illegible]
20 Ratshin R. A Hunt D Russell J & Rackley C E. QT interval prolongation, [illegible] and ventricular arrhythmias and [illegible] Ann Intern Med 75 919 1971
21 Schwartz, P J & Malliani A. Electrical [illegible] the T wave: clinical and experimental [illegible] relationship with the sympathetic nervous [illegible] the long Q-T syndrome Am Heart J [illegible]
22 Selzer A. & Wray H. W Quinidine syncope [illegible] lation 30 17 1964
23 Theisen K. Haider M & Jahrmarker H [illegible]suchungen uber ventrikulare Tachykardien [illegible] entry bei inhomogener *Repolarisation*. Dtsch Wochenschr 100 1099 1975
24 Vincent G M [illegible] Abildskov J A. & Burgess [illegible] Q-T interval syndromes. Prog Cardiovasc [illegible] 523 1974

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24-Hour Blood Glucose Profiles in Insulin-Dependent Diabetics Treated with Intravenous Insulin Infusion Systems

A Comparison between Closed and Open Loop Systems

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Per Aaby Svendsen and Allan Renard Andersen

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Finsen Institute Copenhagen Denmark*

RACT The aim of this study was to compare 4-hour blood glucose profiles of insulin-depend abetics during treatment with preprogramed n delivery systems with those of patients on ment with the artificial beta cell (Biostator®) blood glucose (MGB) was 4 4±0.5 mmol/l for trols, 5 8±1 0 for 53 patients on open loop and 16 for 20 patients on closed loop treatment was significantly higher in diabetics than in iabetics but the difference between the two ic populations was not significant Mean tude of blood glucose excursion was 1.8±0 6 l3 and 3.5±0 8 mmol/l respectively, the differ between the diabetic groups being significant. oglycemia was seen in patients during closed treatment whereas this was the case in 10 of 53 ts on treatment with open-loop systems Physi ercise resulted in small but normal decreases in glucose without hypoglycemia Plasma insulin *within the normal range during both regimes* It cluded that blood glucose control during treat with closed loop system is superior to that dur treatment with open loop systems However, r standard conditions i v insulin infusion with grammed pump devices resulted in blood se fluctuations comparable with those during ator® treatment.

ords artificial beta cell open-loop system closed system plasma insulin insulin-dependent diabetes Med Scand 208 451 1980

…taneous insulin therapy combined with ed food consumption has not normalized the al of insulin-dependent diabetics The mor among insulin-dependent diabetics exceeds ortality of sex and age matched non-diabetics by about 600% (11) In western countries this depressing prognosis is caused by development of nephropathy myocardial infarction and vascular cerebral insults complications which beside re tinopathy and neuropathy seem to be the result of deficient restoration of metabolic and endocrine abnormalities in the patients

Permanent restoration of normal metabolic and hormonal conditions in diabetics without endogen ous insulin secretion is extremely difficult because 1) The postprandial plasma insulin peak in normals cannot be fully imitated even by subcutaneous in jection of regular insulin (Fig 1) 2) The reproduci bility of absorption of insulin suspensions from sub-cutaneous tissue is too low (coefficient of variation 26%) (17) 3) Exercise increases the subcutaneous blood flow and thereby absorption of insulin (18) 4) Regular life with planned meals (which is necessary in insulin treated patients in order to avoid severe hyper and hypoglycemia) constitutes an unac ceptable reduction of individual freedom for many patients

Furthermore incorrect measurements of the in sulin amount in the syringe (20) reflux of insulin from the injection channel (20) subcutaneous de gradation of injected insulin (3 9) variations in insulin absorption rate between different areas of the body (4) and different tissue depths and varia tions in the motility of the stomach contribute to these difficulties Also 1–3 injections a day are disturbing and may give rise to lipodystrophy aller gy and pain

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Abbreviation. IRI = immunoreactive insulin MBG = mean blood glucose MAGF = mean amplitude of glyce mic excursions

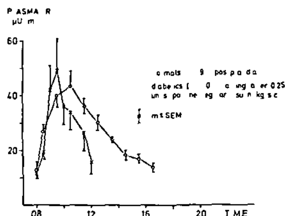


Fig 1 Comparison of plasma IRI between 9 non d abet cs after breakfast and 10 fasting d abet cs after subcutaneous inject on of 0 25 U porcine regular insulin/kg b wt (mean ± S E M)

In order to avoid hypoglycemia and unpredicted hyperglycemia self monitoring of blood glucose has been introduced with good results in selected patient series (33) However in a prospective study of consecutive insulin dependent diabetics with newly detected simplex retinopathy Andersen et al (2) did not achieve normalization of blood glu cose profiles by this method Therefore and be cause of the severe draw back of the subcutaneous insulin therapy mentioned i v insul n infusion sys tems are under evaluation in several places (1 15 16 21) The a m of this paper is to compare the effects of two i v insulin infusion systems the so called closed and open loop system on glycemic regulation of insulin dependent diabetics in short term experiments

SUBJECTS AND METHODS

losed loop system Twenty non obese insul n dependent diabetics (3 females and 17 males aged 18–46 years) who had had diabetes for 3–29 years were exam ned under ward cond t ons after several days of attempt to ach eve metabolic control with subcutaneous insul n therapy In formed consent was obta ned from all after careful expla nat on of the nature and purpose of the nvest gat on The cl n cal data appear from Table I

Remain ng endogenous nsul n secret on was est mated by determ nat on of human plasma C pept de before and after an i v inject on of 1 0 mg glucagon (Novo) by the method of Faber (12) C pept de was not found in any of the 19 pat ents tested They had been treated w th h ghly purif ed porcine NPH insul n (Retard® Nordisk Insul n lab) for several years most of them w th injections tw ce a day The daily insulin dose varied between 0 40 and 1 28 U/kg b wt None of the pat ents had acute llnesses

The d et was str ctly planned and served at exa same time of the day in all exper ments breakf a m lunch at 12 a m d nner at 6 p m snacks at p m The compos t on and amount of nd dua var ed greatly accord ng to the hab ts of each pat general about 30% of the daily amount of bread w at 8 a m 40% at noon 10% at 7 p m and 0 a The hot meal at 6 p m was served w th or potatoes but always w th vegetables A 30-m n erg b cycle r de was performed by every pat ent at 10 and at 3 p m

Ope loop syste i Fifty three insul n-depend bet cs (19 females and 34 males aged 14–56 yea d abetes for 4–39 years and deal we ght of 75–134 examined under the above cond t ons These were comparable w th those n the clo ed loop g gard ng age durat on of d abetes body we ght tr and compl cations (Table I)

C pept de was found n one of the 35 cases wl tested for glucagon In this case only a very sl s gn f cant increase n C pept de was demon ra e after glucagon nject on (0 08→0 14 pmol/ml) comp 0 36→1 78 pmol/ml n normals (12) The 35 pat whom C pept de was measured d d not de iate fr others regard ng age durat on of d abetes body w nsul n dose The daily nsul n dose var ed betwe and 1 30 U/kg b wt The d et and phys cal exerc e the exper ments were as descr bed abo e

C ols F fteen non-obese non d abet c o (ideal body weight 97 9% age 13–48 years (mean d abetic d et served as normal controls Plas munoreactive insul n (IRI) fluctuat ons were meas 9 of them

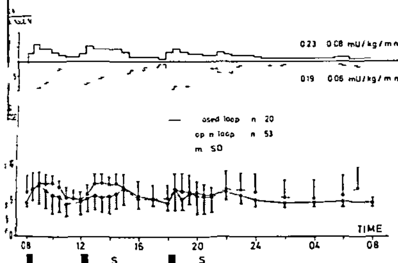
Exper mental des gn

When informed consent had been obtained NPH treatment was d scont nued and regular n u n w ministered subcutaneously 4 t mes daily n o der t me for el m nat on of NPH nsul n from the subcut tissue before in t at on of nsul n nfus on

The pat ents were connected to an artificial (closed loop B ostator® M les) or a portable nsul s on pump (open loop system descr bed elsewhere least 6 hours before the start of metabol c measure

The cal brat on of the art f cial B-cell s descr deta l elsewhere (8) and algor thms were set to g least amount of nsul n wh ch could normal ze t tolerance in juven le d abet cs (KR 0 Ql 40 Tl amount of glucose infused with B ostator was 0 hours Basal insul n infus on was def ned as the amount of insul n infused per kg per min betwe a m and 5 00 a m

Insul n nfus on w th the portable nfusion pum preprogramed accord ng to the follow ng gu delin 8–10 a m 17% of the total da ly amount of nsul infused at 10–12 8% of the total da ly nsulin an 12 14 17% at 14–16 8% at 16–18 5% at 18– 0 at 20–22 8% Between 22 and 08 0 % of the tot nsul n amount was nfused Only small varia ions program were perm tted The nsul n concentration solut on n the nfus on syringe var ed howe er



Capillary blood glucose in 53 insulin-dependent [diabet]ics treated with open loop system and venous blood [glucos]e in 20 insulin-dependent diabetics treated with [closed]-loop system ($M \pm S$ D) compared to capillary blood glucose in 15 non-diabetics on diabetic diet ($M \pm 2$ S D) (shaded area) Insulin infusion rate in relation to basal infusion is given on the top Mean basal insulin infusion rate is given in the figure

[betw]een patients depending on the individual daily insulin [require]ment which was calculated on the basis of several [outpati]ent visits and observations during hospitalization [...] patients in the open loop group performed physical [exerci]se of moderate severity on a bicycle ergometer (in[crease] in heart rate about 40%) during fast and constant [insuli]n infusion rate Seventeen patients in the closed loop [group] performed physical exercise of similar severity dur[ing po]stprandial state three hours after a main meal and [one ho]ur after a snack

[Ven]ous blood glucose was measured continuously by the [analy]zor in the closed loop system In order to make [compa]risons with the open loop system mean blood glu[cose (]MBG) of the last 5 min before the time given in Fig 2 [was d]etermined in each case During experiments in the [open]-loop system capillary blood was taken from the [...]be 30 times a day for whole blood glucose determination by the glucose oxidase method (34) Sampling hours are given in Fig 2 Glucose in 24-hour urine samples was also determined by the glucose oxidase method MBG (± S D) was calculated on the basis of all capillary blood glucose determinations per 24 hours As a measure of blood glucose fluctuations in the individual patient the mean amplitude of glycemic excursions (MAGE) was calculated by the method of Service et al (28) Hypoglycemic reactions were recorded when the patient had appropriate symptoms and blood glucose levels lower than 2 5 mmol/l

Plasma IRI was measured by the method of Heding (14) in 4 ketotic newly diagnosed diabetics in the open loop group during i v insulin infusion and in those 14 of the 20 closed loop patients who had no or only minimal amounts of insulin antibodies

Statistical evaluation was carried out by Students *t* test

[Tab]le 1 *Clinical data on the patients (mean ± S D)*

	Closed loop group (n=20)	Open loop group (n 53)
[Age] (y)	32 3±9 6	31 6+11 6
[Dura]tion of diabetes (y)	11 4±6 8	15 9+7 7
[%] ideal body weight	95 0±9 1	99 5+11 8
[Insuli]n/kg b wt subcutaneously (U)	0 73±0 22	0 67+0 24
[Calori]es ingested	2 117±301	1 889±303
[No] of pats with		
[Ret]inopathy	9	29
[Ne]phropathy	1	3
[Ne]uropathy	6	25

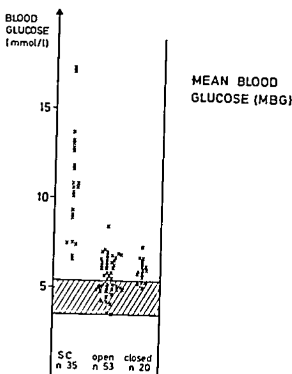


Fig 3 Individual MBG in insulin-dependent diabetics on subcutaneous insulin therpay (*s c*) treated with the open loop or the closed loop system Shaded area = $M \pm 2$ S D of 15 non-diabetics

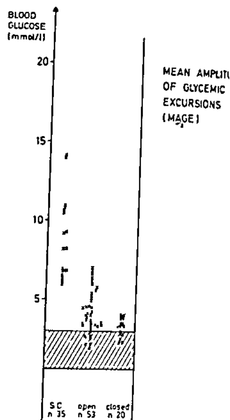


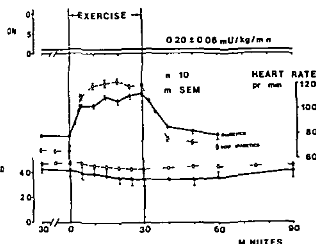
Fig 4 Individual MAGE in the same patients as in Shaded area = $M \pm 2$ S D of 15 non-diabetics

RESULTS

Fig 2 shows the blood glucose variation during 24 hours of insulin infusion both with the closed loop and the open loop system Most of the time MBG was within the normal range In the daytime the open loop system gave lower blood glucose values whereas they approached the physiological with the closed loop system in the night. F shows the individual MBG values during in infusion MBG values for 35 of 53 patients underwent the same blood glucose measure schedule as on the experimental day on the last

Table II *Insulin infusion rate insulin requirement MBG MAGE glucosuria and hypoglycemi sulin dependent diabetics treated with closed loop and open loop insulin infusion systems*

	Control group ($n=15$)	Closed loop group ($n=20$)	Open loop group ($n=53$)	Significance of the difference closed/open loop
Basal insulin infusion rate (mU/kg/min)		0 23±0 08	0 19±0 06	n s
Maximal infusion rate (% of basal)		570	900	–
Total insulin amount (U/24 h)				
Subcutaneous		48 6±11 6	44 6±11 9	n s
I v infusion		47 9±12 2	44 4±12 8	n s
MBG (mmol/l)	4 4±0 5	6 0±0 6	5 8±1 0	n s
MAGE (mmol/l)	1 8±0 6	3 5±0 8	4 3±1 3	$2p<0.02$
Glucosuria (g/24 h) (range)		0–5	0–16	n s
Hypoglycemia (n)		0	10	–



F g 5 Cap llary blood glucose (M + S E M) before during and after phys cal exerc se n 10 fast ng nsul n-dependent *d abet cs treated w th the open loop system* (●—●) and 10 non-diabet cs (O— —O)

NPH *treatment are given for com*

Apparently many of the pat ents infused the open loop systems had values w th n the al range whereas only few infused w th the ed loop systems were brought down to such ls However the d fference n MBG between two systems was not s gn f cant (Table II)

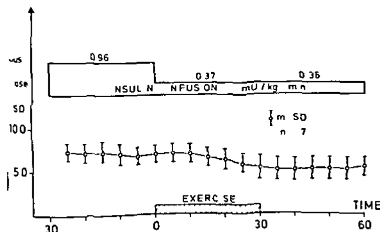
he MAGE d d not normalize in most pat ents w th the closed or the open loop system (Fig but improved cons derably compared to the pat ent s values when treated w th subcutane insul n suspens ons It should be noted that GE does not normalize n patients on closed system MAGEs were s gn ficantly higher in loop than in the closed loop group (Ta)

ere hypoglycem c attacks were not seen n group However 10 of the 53 pat ents n the loop group reported hypoglycem c feel ngs together w th cap llary blood glucose values below ? 5 mmol/l Some of the ?0 pat ents in the closed loop group received glucose by the B ostator in order to avo d hypoglycem a but the dose never exceeded ? g/?4 hours

Urinary glucose excret on was 0–16 g/?4 hours (mean ? 8) n pat ents in the open loop group and 0–5 g/?4 hours (mean 1 0) in the closed loop group (Table II)

Cap llary blood glucose concentration in 10 open loop group patients perform ng phys cal exer cise during fast decreased only sl ghtly in sp te of a rather heavy work load w th pulse increments of 40% (F g 5) *Postprand al exercise 3 hours after a* ma n meal and one hour after snacks in the closed loop group led also to a small but sign f cant de crease n venous blood glucose n 17 pat ents (F g 6) in sp te of decreas ng nsul n nfus on rates

There was no d fference in e ther group between



F g 6 Venous blood glucose (M + S D) before during and after phys cal exerc se n 17 nsul n dependent d abetics 3 hours after a main meal and one hour after a snack The pat ents were trea ed w h a closed loop system n wh h the nsul n nfus on rate was dependent on blood glucose concentrat on The amount of nsul n infused 30 m n before during and 30 m n after phys cal exerc se was n egra ed The ef fect of phys cal exerc se on insu- l n requ rement s ob ous

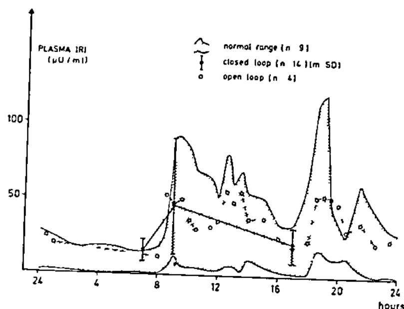


Fig 7 Plasma IRI in the fa[sting] state (07 00 a m) postpra[ndial] (09 00 a m) and before d[inner] (05 00 p m) in 14 insul[i]n-d[ependent] diabetics (●—●) on closed [loop] treatment ($M \pm S$ D) and 4 patients with newly d[i]agno[sed in]sulin-dependent diabetes on [open] loop treatment (O---O) [in] compared to the plasma IRI in 9 non-obese non-diabet[ics on] diabetic diet (shaded area)

the total amount of insulin given on the last day of NPH treatment and on the infusion day (Table II) The basal insulin infusion rate (amount of insulin infused per kg/min between 1 and 5 a m) was the same in the two systems The increase in infusion rate in per cent of the basal infusion was similar in the two systems (Fig 2) and plasma insulin con centration was within the physiological range dur ing infusion in both systems (Fig 7)

DISCUSSION

The results demonstrated that the closed loop and open loop systems gave almost equally good blood glucose profiles in insulin depdendent diabetics During daytime blood glucose was lower in patients on treatment with open loop than closed loop sys tem In the night however it was the other way round This is in accordance with the different infusion rates in the two systems the open loop system infusing more insulin in connection with the main meals (Fig 2) By changing the constants of the Biostator® better results could possibly be achieved but only by infusion of larger amounts of insulin A second possibility that might result in normalization of MBG and MAGE without incre ment of the amount of insulin infused would be to preprogram the closed loop system to increase the insulin infusion at the very beginning of meals The standard deviation of MBG is lower in patients treated with the closed loop system and also the MAGE of closed loop system patients seems to be more physiological than in patients treated with the open loop system The unphysiologically [high] MAGE in patients treated with the closed lo[op sys]tem might reflect the instability of the gl[ucose] oxidase membrane and problems with the sampling catheter

Physical exercise during fasting conditions [with] low constant insulin infusion resulted in a slight decrease in the capillary blood glucose [con]centration Postprandial exercise performed [when] the insulin infusion is high may however lead [to] considerable decrease in blood glucose concen[tra]tions if the infusion rate of insulin is not pr[omptly] decreased as it was in our experiments

The infused amount of insulin did not differ [from] that given subcutaneously This does not rule [out] the possibility of slight subcutaneous insulin de[gra]dations (9) since the subcutaneously adminis[tered] insulin dose should eventually have been a [little] higher in order to achieve better metabolic reg[ula]tion

Plasma insulin concentrations during infu[sion] were within the normal range This is in accorda[nce] with findings by others (27 29) Thus it does [not] seem necessary to induce peripheral hype[rin]sulinemia during i v insulin infusion in order [to] normalize blood glucose in insulin-dependent [dia]betics without endogenous insulin secretion [as] claimed by Botz et al (7)

Long term infusion of insulin has been d[em]onstrated to normalize not only plasma blood [glu]cose concentration but also other metabolites [and] hormones (22 23 31 32) often found in [un]physiological amounts in insulin treated diabe[tics]

ubcutaneous insulin injection therapy Long i.v infusion is however not realistic since ation of catheters in the subclavian vein for term use is reported to have a frequency of plications between 0 5 and 8% (25) sepsis ating from these catheters has been found in 0 8–1 6 years of catheter application (19 Furthermore the frequency of tromboses and mbolism cannot be neglected Intraperitoneal cation of insulin infusion is therefore under ideration (24 26)

bcutaneous insulin infusions have been inves d by several groups (23 31 32) However the s of blood glucose regulation in insulin-depen diabetics without endogenous insulin secretion not as good as those of i v infusions probably ue the reproducibility of the absorption of in from the subcutaneous tissue is not good h and because it takes too much time before a insulin peak concentration is achieved after re wave pulse from the infusion system (30) ce implantable closed loop systems can prob- not be constructed in the near future mainly o difficulties with the glucose sensor min ed pumps for implantation applicable for loop systems are now being constructed (5 uch pumps should be constructed with at least rograms of infusion profiles which could be ted by the patient himself since only one pro- turned out to be insufficient for insulin-depen diabetics on totally free diet (10) Another dif might be the insulin concentration in the on in the reservoir of such pumps In our atory a solution of highly purified porcine n 500 U/ml was stable at 37°C for several hs A precipitation of insulin might however during agitation of such solution Studies are ogress to solve these problems

CONCLUSION

r standard conditions (planned meals and se) closed loop as well as open loop systems ring blood glucose and plasma insulin near the al range in insulin dependent diabetics without genous insulin secretion Blood glucose con with the closed loop system is however rior to that with the open loop system since standard deviations of MBG and MAGE are ler with the former than with the latter system risk of developing severe hypoglycemia during exercise seems to be small but it has to be found out whether blood glucose fluctuations resulting from improvisations regarding time and quantity of meals during daily life can be regulated by open loop infusion pumps

REFERENCES

1 Albisser A M Botz C K & Leibel B S Blood glucose regulation using an open loop insulin delivery system in pancreactectomized dogs given glucose infusions Diabetologia 16 129–133 1979
2 Andersen A R. Andersen J K Lorup B Frost Larsen K Christiansen J S & Deckert T Selvbe stemmelse af blodglukosekoncentrationen ved in sulinafhængig diabetes Ugeskr Laeger 32 2038–2042 1980
3 Berger M Halban P A Girardier L Seydoux J Offord R E & Renold A E Absorption kinetics of subcutaneously injected insulin Diabetologia 17 97–99 1979
4 Binder C Absorption of injected insulin Munksgaard Copenhagen 1969
5 Blackshear P J Rohde T D Grotting J C Dorman F D Perkins P R Varco R L & Buchwald H Control of blood glucose in experimental diabetes by means of a totally implantable insulin infusion device Diabetes 28 634–639 1979
6 Bojsen J Kølendorf K Haslev F & Jørgensen K A portable infusion pump programmable with 16 rates Biotelemetry 5 123–133 1978
7 Botz C K Marliss E B & Albisser A M Blood glucose regulation using closed and open loop insulin delivery systems Diabetologia 17 45–49 1979
8 Christiansen J S Svendsen P A Soegaard U & Frandsen M Tests of analyzer and infusion system of an artificial betacell (Biostator®) Acta Diabetol Lat. In press 1980
9 Dandona P Foster M Healey F Greenbury E & Beckett A G Low-dose insulin infusions in diabetic patients with high insulin requirements Lancet 2 283–285 1978
10 Deckert T Bojsen J Kølendorf K Lørup B & Deckert M Programmed insulin delivery Excerpta Med Int Congr Ser 500 649–654 1980
11 Deckert T Poulsen J E & Larsen M Prognosis of diabetics with diabetes onset before the age of thirtyone Diabetologia 14 363–377 1978
12 Faber O K & Binder C C peptide response to glucagon Diabetes 26 605–610 1977
13 Frankel B J Schmid F G & Grodsky G M Effect on continuous insulin infusion with an implantable seven-day minipump in the diabetic Chinese hamster Endocrinology 104 1532–1539 1979
14 Heding L. Determination of total serum insulin (IRI) in insulin treated diabetic patients Diabetologia 8 260–266 1972
15 Hepp K D Renner R Franetzki M & Mehnert H Substitution of islet-cell function with "open loop" insulin infusion system Adv Exp Med 119 485–489 1979

16 Irsigler K & Kritz H Long term cont nuous n travenous nsul n therapy with a portable nsul n dos age regulat ng apparatus D abetes 28 196–203 1979
17 Kølendorf K Aaby P Westergaard S & Deckert T Absorption effect veness and s de effects of h ghly purif ed porcine NPH nsul n preparat ons (Leo®) Eur J Cl n Pharmacol 14 117 1?4 1978
18 Kølendorf K Bojsen J & Nielsen S L Ad pose t ssue blood flow and nsul n d sappearance from subcutaneous t ssue Cl n Pharmacol Ther 25 598–604 1979
19 Ladefoged K & Jarnum S Long term parenteral nutrit on Br Med J 2 ?6? ?66 1978
20 N elsen V Insul ndosering Ugeskr Laeger 4 ?25 229 1980
21 Pfeiffer E F Thum Ch & Clemens A H The artificial beta cell—A cont nuous control of blood sugar by external regulat on of insul n nfus on (glu cose controlled nsul n nfus on system) Horm Metab Res 487 339–342 1974
22 P ckup J C Keen H Parsons J A & Alberti K G M M Cont nuous subcutaneous insulin nfus on Good blood glucose control for up to 4 days D abetolog a 16 385 389 1979
23 P ckup J C Keen H Parsons J A Alberti K G M M & Rowe A S Cont nuous subcutaneous nsu lin infus on Improved blood glucose and inter med ary metabol te control n d abet cs Lancet I 1251 1257 1979
24 Poulsen J S D Sm th M Deckert M & Deckert T Intraperitoneal insul n infus on Acta Endocrinol 95 1980
25 Ryan J A Abel R M Abbott W M Hopk ns C C Chesney T McC Colley R Ph l ps K & F scher J E Catheter compl cat ons n total parenteral nutrition A prospect e study of 00 conse pat ents N Engl J Med 90 757 61 19 4
?6 Schade D S Eaton R P Spencer W Go R & Co bett W T The per oneal absorp nsul n d abet c man A poten al s te f r a me l insul n del ery system Metabol m 3 195–19
27 Serv ce F J Normal zat on of p a ma glu unstable d abetes Stud es under ambul r cond t ons w th pumped ntra enous n u in Cl n Med 91 480–489 1978
?8 Se v ce F J Molnar G D Rose ar J W Kerman E Gatewood L C & Taylo W R ampl tude of glycem c excurs ons a mea ure bet c instab l ty D abetes 19 644–655 19 0
?9 Sh ch ri M Kawamor R & Abe H Nor tion of the paradox c secret on of glucagon n dia who we e controlled by the artif c al be a cel betes 28 ?7? ?75 1979
30 Slama G Buu K m Nguyen Phuoc Tchob o G Delage A & Desplanque N and C pept de levels during cont nuou subcut nsul n nfus on D abetes Care 3 51 55 19?
31 Tamborlane W V Sherw n R S Genel Fel g P Restorat on of normal and amin metabol sm n diabet c pat ents t ea ed w th a p insul n nfus on pump Lancet I 1 58–1 61
3? — Reduct on to normal of plasma glucose d abetes by subcutaneous adm n s ra ion of with a portable nfus on pump N Engl J Med I 578 1979
33 Tattersall R B Home blood glucose D abetolog a 16 71 74 1979
34 Tr nder P Determ nat on of g uco e n b oo glucose ox dase w th an alterna e oxygen a Ann Cl n B ochem 6 ?4–?7 1969

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Studies on Hemopoietic L lasia (the Preleukemic Synd me)

Cl cal Course and Prognostic Factors in 42 P t t st c Bone Marro

Jan Lidbeck

From the Department of Internal Med c ne Un H p L k p ng S eden

RACT The clinical course of 42 patients with oietic dysplasia diagnosed during 1974–77 has studied The clinical, laboratory and mor ical findings at presentation were investigated gnostic significance At the time of completion study (Aug 1979), 38% had developed acute ia (median survival after diagnosis 5 months) % had d ed of complications (bleeding and in s) due to severe cytopenia (median survival 6) An overall malignant course was observed in s with low platelet count ($<80\times10^9$/l) bleed d a severe myeloid maturation defect in the narrow (>30% myeloblasts and promyelo- Increased serum vitamin B and presence of lasts promyelocytes and abnormal mono- cells in the peripheral blood indicated a leu ermination

ds hemopo et c dysplasia, preleukem a cl n cal prognost c factors

d Scand 208 459 1980

o et c dysplasia (HD the preleukem c syn is a disorder with a high mortal ty rate (1 3 terminates frequently in acute myel d a (AML) A number of factors bel eved to ognostic s gnificance have been described in t ents Severe anemia (8 13) reduced count (8 17 20) chromosomal abnormal 13 14 17) absence of typ cal ringed asts (6) or increasing numbers of myelo- the bone marrow (7 8 12) have been re to ind cate an increased risk of acute c transformation However many patients develop leukemia but succumb from the of severe cytopenia and some appear to n gn course (11 18) over several years cl nical laboratory and morphol gic l fea patients with dysplastic bone marrow have amined and are presented n this study Parameters assumed to be of prognostic value were compared and related to the time of survival in patients who developed leukemia and pat ents who died of cytopenia

PATIENTS AND METHODS

Forty two pat ents (25 men and 17 women mean age 69 years) who had presented with dysplast c bone marrow at our department n 1974–77 were stud ed The def n tion of HD in this nvest gat on included pat ents w th both normal and ncreased numbers of myeloblasts and promyelocytes n the bone marrow (V lter et al 1967 Type I and Type III refractory anem a Dreyfus et al 1970 Refractory anem a w th excess of myeloblasts) The deta ls of def n t on and the pat ents exam ned have been described elsewhere (9)

Parameters examined

The cl nical and laboratory parameters exam ned for p ognost c s gn f cance were a h story of hemorrhag c ep sodes and/or recurrent nfections hemoglobin (Hb <80 g/l wh te blood cell count (WBC) $<2.5\times10^9$/l platelet count $<80\times10^9$/l mean corpuscular volume (MCV) ncreased serum v tam n B_{12} serum ron re t cul cyte count lactate dehydrogenase (LD) and mor phol g cal abnormal t es n the blood and bone marrow For evaluat on of the myelo d maturat on defect n the b ne ma row a 4 graded scale was used referr ng to the relat ve number of myeloblasts and promyelocytes w th n the ranges 8–19 20–29 30–39 and 40–50%

The parameters under considerat on were 1) exam ned n ( ) pat ents who developed acute leukem a and (*b*) pat ents who d ed of HD w thout leukem c transfo mat on 2) Related to a surv val f (*a*) less than 3 months (*b*) 3–12 months (*c*) more than 12 months after d agnosis

The stat st cal methods used we e F her s exact test and the Fourfold table test

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Abbre ions AML = acute myelo d leukem a AMMI = acute myelomonocyt c leukem a EL = ery roleukemia Hb = hemoglob n HD = hemo dysplas a LD = lactate dehydrogenase MC co puscular v lume WBC = wh te bl od cel

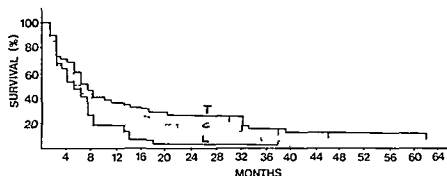


Fig 1 Survival from t[he] time of diagnosis T = [...] series C = patients wh[o] ... of cytopenic complicati[ons] L = patients who devel[oped] acute leukemia. Short [verti]cal lines indicate patien[ts] alive

RESULTS

When the clinical and morphological examination had been completed (Dec 1977) 31 patients had died Thirteen deaths were due to acute leukemia (7 AML 4 acute myelomonocytic leukemia (AMML) 2 erythroleukemia (EL)) and 18 due to complications of cytopenia (bleeding infection) One year later 5 more patients had died (3 of AML and one each of severe cytopenia and myocardial infarction) Of the 17 patients (40%) who until Aug 1979 had developed leukemia only one (a male aged 36) entered remission after chemotherapy and he is still alive The median survival estimated from the diagnosis of HD was 7 months (mean 23) 5 months (mean 14) for the patients who developed acute leukemia and 6 months (mean 32) for those who died in HD (Table I) Five patients with a stable dysplasia are still alive 30–62 months after diagnosis (Fig 1)

Prognostic factors

Parameters of significance in varying prognostic categories (Table II) were 1) Patients who developed acute leukemia differed from those who died of HD in (*a*) number of patients with increased serum vitamin B_{12} (10/16 vs 1/14 $p<0.01$) and (*b*) number of patients with myeloblast[s] myelocytes *and* abnormal monocytoid cells i[n] blood (6/17 vs 1/19 $p<0.05$) 2) Patients wh[o sur]vived less than 3 months after presentation d[iffered] from those who survived 3–12 months i[n] number of patients with a history of hemor[rhagic] episodes (10/12 vs 5/15 $p<0.05$) and (*b*) n[umber] of patients with ≥30% myeloblasts and pro[myelo]cytes in the bone marrow (11/12 vs 4/15 $p<$

Patients who survived less than 12 mont[hs dif]fered from those who survived longer (includ[ing] 5 dysplastic patients still alive) in (*a*) num[ber of] patients with bleedings (15/27 vs 2/13 $p<0.0$ ... *number of patients with a platelet count* <80 ... (14/27 vs 2/13 $p<0.05$) and (*c*) number of p[atients] with ≥30% myeloblasts and promyelocytes [in] bone marrow (15/27 vs 0/13 $p<0.001$)

Other clinical and laboratory paramete[rs ex]amined (a history of recurrent infections H[b] ... g/l WBC $<2.5\times10^9$/l increased MCV serum ... reticulocyte count and LD) or other blood c[ell fea]tures (severe red cell abnormalities prese[nce of] immature myeloid or monocytoid cells) and ... marrow abnormalities (dyserythropoietic fe[atures] myeloid cellular abnormalities megakaryo[cytic] maturation defects) did not differ significantly

Table I *Clinical course of the 42 patients*

Present state	N	%	Clinical outcome	N	%	Final complications: Bleedings	Final complications: Infections	Median survival (mo)*
Dead	36	86	AML/AMML/EL	16	38	4	8	5 (14 1–3[...])
			HD	19	45	9	13	6 (3[...] 4–5[...])
			Myocardial infarction	1				38
Alive	6	14	AML in remission	1				38 (41 30–[...])
			HD	5				

* Mean and range given in parentheses

...ell Prognostic factors

	Development of leukemia (n=17)	Dead in dysplasia (n=19)	Survival (mo)* <3	3–12	<12	>12
...ased serum B_{12}	10/16	1/14*	5/8	5/15	10/23	1/10
...oblasts promyelocytes and ...ocytoid cells in the blood	6/17*	1/19	3/12	3/15	6/27	2/13
...ings	10/17	6/19	10/12*	5/15*	15/27	2/13
...let count <60×10⁹/l	6/17	10/19	9/12	5/15	14/27*	2/13*
...e marrow myeloblasts and ...myelocytes ≥30%	8/17	6/19	11/12 *	4/15**	15/27 *	0/13*

...amined in 33 patients only
...o patients (one who died of myocardial infarction and another with AML in remission) were excluded from the ...uation
...0.05 ** $p<0.01$ *** $p<0.001$

...ed in the different patient groups or when related to the time of survival

DISCUSSION

...mopoietic dysplasia transforms into acute my...d leukemia in about 3/4 of patients within 2 ...rs after diagnosis (11). However as much as ...0% (2 12) have been reported to die from ...openic complications a finding largely in agree...nt with this study. Thus HD has a high overall ...tality rate which has so far reached near 90% in present examination.

...he median survival time of 7 months in this ...y differs from that of 26 months reported by ...mpel et al (7) and there is a considerable varia... in the survival of patients with HD. In the ...ent study one patient died only one month after ...gnosis and another is still alive and well after 5 ...rs. Extremely long and benign courses up to 17 years have been reported (10 14 15). How... such patients may still have an increased risk ... a fatal outcome with or without developing ...kemia (1) and should be controlled as regularly ...those with a more rapid course.

Some parameters of possible prognostic signifi...ce have been demonstrated (*Table II*) a few of ...uch (reduced platelet count and myeloid bone ...row maturation defect) are in accordance with ...ther studies. However it was somewhat un...eseen to find an increased serum vitamin B_{12} ...re frequently in patients who developed leu...mia than in those who did not. It has been ...gested (14) that an elevated serum B_{12} might be ...e to increased promyelocytes in the bone marrow (transcobalamin I is believed to be a product of the granules of promyelocytes) and serum B_{12} has been reported to be elevated in some patients with acute leukemia (16). The increased vitamin B_{12} found in some HD patients might reflect the myeloid maturation defect at a stage when many of the myeloid cells are promyelocytes.

In this study patients with low platelet count bleedings and a severe maturation defect (≥30% myeloblasts and promyelocytes) in the bone marrow appeared to run a malignant course with short survival. Thus the evaluation of such simple clinical parameters can be of some prognostic value and can also be used in hospitals without specialized hematological units. However the prediction of the clinical outcome from laboratory and morphological data might not be quite reliable but the use of modern methods such as in vitro culture of granulopoietic stem cells (4 19) has added more reliability to the prediction of the clinical course in HD. In vitro culture studies in combination with morphological examination might increase the possibility to predict the course. Such studies are in progress.

REFERENCES

1. Block M, Jacobson L O & Bethard W F. Preleukemic acute human leukemia. JAMA 152 1018 1953
2. Dreyfus B. Preleukemic states. I Definition and classification. II Refractory anemia with an excess of myeloblasts in the bone marrow (smouldering acute leukemia). Blood Cells 2 33 1976
3. Dreyfus B, Rochant H, Sultan C, Clauvel G P, Yvart G & Chesneau A M. Les anémies

taires avec exces de myeloblastes dans la moelle Etude de 11 observations Presse Med 78 359 1970
4 Faille A Dresch C Poirier O Balitrand N & Najean Y Prognostic value of in vitro bone marrow culture in refractory anemia with excess of myelo blasts Scand J Haematol 20 280 1978
5 Goldstone A H Cawley J C & Hayhoe F G Leukaemias lymphomas and allied disorders Saun ders London 1976
6 Hast R Studies on human preleukemia IV Clinical and prognostic significance of sideroblasts in are generative anaemia with hypercellular bone mar row Scand J Haematol 21 396 1978
7 Heimpel H Drings P Mitrou P & Queisser W Verlauf und prognostische Kriterien bei Patienten mit Praleukemie Ergebnisse einer prospektiven Studie Klin Wochenschr 57 21 1979
8 Izrael V Jacquillat C Chastaing G Weil M De Heaulme M Boiron M & Bernard J Donnees nouvelles sur les leucemies oligoblastiques A propos d une analyse de 120 cas Nouv Presse Med 4 947 1975
9 Lidbeck J In vitro colony and cluster growth in hemopoietic dysplasia (the preleukemic syndrome) I Clinical correlations Scand J Haematol 24 412 1980
10 Linman J W Myelomonocytic leukemia and its preleukemic phase J Chron Dis 22 713 1970
11 Linman J W & Bagby G C Jr The preleukemic syndrome (hemopoietic dysplasia) Cancer 42 854 1978
12 Najean Y Pecking A & Broquet M Anémies refractaires avec myeloblastose partielle (I) Analyse d une protocole groupant 79 cas I—Cara cliniques et evolution sous androgenotherapie Rev Fr Hematol 16 67 1976
13 Nowell P C Marrow chromosome studies in leukemia Cancer 28 513 1971
14 Pierre R V Cytogenetic studies in preleuk Studies before and after transition to acute leu in 17 subjects Blood Cells 1 163 1975
15 Pretlow T G Chronic monocytic dyscrasia nating in acute leukemia Am J Med 46 130 19
16 Rachmilewitz D Rachmilewitz E A Pollia & Hershko Ch Acute promyelocyte leukem report of five cases with a comment on the d tic significance of serum B_{12} determination Haematol 22 87 1972
17 Ricci P Baccarani M Zaccaria A Santuc A & Tura S Clinical contribution to the know of hemopoietic dysplasias Long term follow up patients with refractory anemia. Acta Hae 60 10 1978
18 Saarni M J & Linman J W Preleukemia hematological syndrome preceding acute leuk Am J Med 55 38 1973
19 Senn J S & Pinkerton P H Defective in colony formation by human bone marrow pre overt leukemia. Br J Haematol 23 277 1972
20 Streeter R F Presant C A & Reinhard E nostic significance of thrombocytosis in idiop sideroblastic anemia Blood 50 427 1977
21 Vilter R W Will J J & Jarrold T Refra anemia with hyperplastic bone marrow (aregener anemia) Semin Hematol 4 175 1967

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Sinus Node Dysfunction in Acute Myocardial Infarction

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[AB]STRACT In a retrospective study of patients ad[mit]ted for acute myocardial infarction (AMI) during [six ye]ars, sinus node dysfunction (SND) was detected [in 29] (1 04%) Twelve had persistent sinus bradycar[dia, e]ll sinoatrial block or sinus arrest and six brady [tach]y syndrome Symptoms occurred in 17 patients [of] whom required temporary pacing for periods [up to t]hree weeks A permanent cardiac pacemaker [was] implanted in three patients with brady tachy [...] Three patients died during the primary [...] d six during the observation period Fol[low-u]p after a mean observation period of 34 months [reveale]d continuous signs of SND in 11 out of 19 pa[tients] The arrhythmia caused symptoms in five pa[tients], two of whom had a cardiac pacemaker and [re]ceived medical treatment It is concluded that [SND] appearing during an AMI persists in a high [numb]er of these patients

[Key w]ords sinus node dysfunction acute myocardial in[farctio]n pacemaker treatment

[Acta M]ed Scand 208 463 1980

[Durin]g the last decade sinus node dysfunction [(SND)] has been increasingly recognized as a cause [of ca]rdiac arrhythmia The various manifestations [of SN]D are known to occur during the acute phase [of my]ocardial infarction (1 2) Parameswaran et al [(3) su]ggested a different persistence of the various [types] of SND particularly the brady tachy syn[drom]e in patients with acute myocardial infarction [(AM]I) The aim of the present study was to find out [whet]her other types of SND carry any prognostic [impli]cations

PATIENTS AND METHODS

[R]ecords of all patients with AMI admitted to the CCU [of th]e University Hospital during a period of approxi[matel]y six years (April 1 1972–Dec 31 1977) were re[viewe]d A definite diagnosis of AMI according to the [WHO] criteria was made in 2789 patients 71 4% of them [were] men The total hospital mortality was 24 7% In all patients the following information was available daily electrocardiogram (ECG) frequent registration of clinical data (blood pressure pulse rate attacks of chest pain administration of analgesic and antiarrhythmic drugs) The cardiac rhythm was monitored continuously for an average of 5–6 days Rhythm strips were recorded automatically in case of bradycardia or tachycardia In addition any changes in cardiac rhythm observed by the technicians could be documented in ECG tracings using a tape recorder with delay

The following ECG criteria for SND were used 1) Persistent sinus bradycardia of less than 50 beats/min during at least 16 hours 2) Sinus rhythm with episodes of sinoatrial block or sinus arrest 3) Brady tachy syndrome i e characteristics as above combined with attacks of tachycardias of supraventricular origin

Patients with previously known SND and those on digoxin β blocking agents or other antiarrhythmic drugs were excluded Patients in whom SND occurred during cardiogenic shock or cardiac resuscitation or was suspected to have been provoked by pain morphine analgesics or vomiting were also excluded

A follow up including patient interview clinical examination X ray of the heart and lungs and one minute 12 lead ECG was carried out in Sept –Oct 1978 Available additional information (records from hospital admission death certificates etc) was also taken into account

RESULTS

Twenty nine patients (5 women and 24 men) met the criteria for SND Some of the clinical data are given in Table I The mean age was 66 years (range 47–83) Previous heart disease was noted in 13 patients (ischaemic in 11 reheumatic in one hypertensive in one) In accordance with the ECG criteria mentioned the cases were divided into three groups

Group I sinus bradycardia (cases 1–12) In five patients the bradycardia was accompanied by minor symptoms (mild hypotension dizziness) but syncopes occurred in one patient with ventricular fibrillation The patients were treated with atropine

Abbreviations SND = sinus node dysfunction AMI = acute myocardial infarction ECG = electrocardiogram

Table I *Clinical data on 29 patients with AMI and SND*

I = inferior A = anterior SB = sinus bradycardia SAB = sinoatrial block SA = sinus arrest AF = atrial f VF = ventricular fibrillation VPB = ventricular premature beats AVB = atrioventricular block VT = ventric cardia SVT = supraventricular tachycardia (+A) = autopsy performed

							Pacemaker treatment		Follow up		
Case no	Sex	Age (y)	Location of AMI	Type of SND	Syncope	Associated arrhythmias	Temporary (d)	Permanent	Observation time (mo)	Type of SND	Causes of death
1	♂	47	I	SB		VPB			42		
2	♂	70	A	SB		AVB 1			55		
3	♂	58	I	SB		VPB			41	SB	
4	♂	52	I	SB					12	SB	
5	♂	67	I	SB		VPB			60		
6	♂	57	A	SB					37	SAB	
7	♂	54	A	SB					16		
8	♂	68	?	SB					17	SB	
9	♂	67	A	SB	+	VF			19	SB	
10	♂	64	I	SB		VPB			16 (†)		Probable M
11	♂	77	A	SB		VPB			25 (†)		Pulmonary oedema
12	♀	69	A	SB					7 (†)		Probable M.
13	♀	71	A	SAB					51	SAB	
14	♂	66	I	SA	+	AVB 3	16		25		
15	♂	63	I	SA SB			10		58	AF	
16	♂	73	I	SAB					27		
17	♂	66	I	SAB SB			4		54	SB	
18	♂	76	A	SA	+	VF	4		25		
19	♀	77	I	SAB					28 (†)		Respiratory ficiency C monale (+
20	♂	59	I	SAB		VPB			-		
21	♂	70	I	SA SB	+	AVB 2	4 (†)				
22	♀	83	I	SA			2 (†)				
23	♂	77	?	SAB					44 (†)		Carcinoma o pancreas (+
24	♂	72	?	SAB AF			10	+	20	Pace rhythm	
25	♀	55	I	SA AF	+	AVB 2	14		18	Paroxysmal AF	
26	♂	64	I	SB AF		VT	3		24		
27	♂	73	I	SA AF	+		3		18 (†)		Carcinoma of colon (+A)
28	♂	59	A	SA SVT	+	VF	7	+ (†)			
29	♂	67	I	SA AF		VPB	23	+	60	AF	

0.5–1.0 mg i.v. resulting in transient increase in heart rate in five. Other arrhythmias and conduction disturbances were noted in seven patients (Table I). The sinus bradycardia lasted for only 1–3 days in most of the patients, yet in two patients throughout their stay in hospital.

Group 2. sinoatrial block/sinus arrest (cases 13–23). This group included 11 patients. SND induced symptoms in six patients, three of whom had one or more syncopes due to sinus arrest. Significant associated arrhythmias appear from Table I. Six patients required temporary pacing, two of these died in cardiogenic shock and four were paced f days. Signs of SND were present during the hospital stay in three patients and during 1–1 in the others.

Group 3. brady-tachy syndrome (cases - All six patients in this group experienced symptoms (syncope, profound hypotension) ing temporary pacing. Treatment with isopre attempted in four patients, failed to maint adequate heart rate. Temporary pacing was tinued for 3–23 days. In three patients it co terminated within two weeks, whereas a perm

II Follow up of 19 patients with SND during

	Group 1	Group 2	Group 3
[illegible]o of pats	12	11	6
deaths	3	4	2
pats followed	9	6	4
[illegible]bservation time			
	32	40	30
pats with signs [illegible]D	5	3	3
[illegible]ent of pats [illegible]ND			
[illegible]	5	2	0
[illegible]d	0	1	1
[illegible]anent pacemaker	0	0	2

[illegible] pacemaker was implanted in three One pa[illegible]ied from ventricular fibrillation on the day [illegible]plantation

[illegible]e entire patient group inferior infarction was [illegible]equent (17 patients) However the ratio of [illegible] to anterior infarction was almost 1 in group [illegible]e a marked predominance of inferior infarc[illegible]s noted in group 2 (8 2) and group 3 (4 1) [illegible]f the 29 patients SND was observed within [illegible]s of the onset of AMI

[illegible]up

[illegible]tient was lost for follow up three died during [illegible]mary admission and six during the observa[illegible]eriod The remaining 19 patients were [illegible]ed after a mean observation period of 34 [illegible] (range 12–60)

[illegible] mortality was 20–25% in each of the three [illegible] (Table II) Extracardiac disease was the [illegible]f death in the three autopsy cases (Table I) [illegible]ath certificates of the three cases without [illegible]y indicated heart disease as the cause of [illegible] No positive indications of systemic em[illegible] or sudden cardiac arrest was given but [illegible]lly the information about these three cases is [illegible]d enough to allow conclusions regarding the [illegible] of death

[illegible]) could be demonstrated by ECG tracings in [illegible]patients In addition two patients had a [illegible]ker Sinus bradycardia (rate 45–50) was [illegible]n five patients and sinoatrial block in two [illegible]atient originally in group 2 (case 15) had [illegible]ped atrial flutter with a slow ventricular rate [illegible]e of treatment with isoprenaline Another pa[illegible]no 25) was treated with quinidine because of paroxysmal atrial fibrillation Apart from these two patients only one namely a patient with sinoatrial block had complaints that could be related to SND The symptoms were insignificant (slight dizziness and palpitation) and the patient managed without any treatment

DISCUSSION

The frequency of SND in AMI patients has been reported to vary from 4 to 5% (1 2 3) This figure is of course dependent on the inclusion and exclusion criteria chosen We found a frequency of 1 04% The retrospective collection of the patient series may have caused some drop-outs but the rather low figure is ascribed particularly to the fact that many cases were excluded because of drug treat ment In accordance with Parameswaran et al (1) we have found a preponderance of inferior infarc tion and onset of SND within the first 24 hours after onset of an AMI in most of our patients Also the finding that treatment with isoprenaline was ineffec tive agrees with the results of Parameswaran et al but not with those of Rokseth and Hatle (2) The latter authors found that temporary pacing was necessary in a few cases only The former authors have pointed out that the treatment of patients with brady tachy syndrome presents particular prob-lems They found that five out of six patients re quired continuous antiarrhythmic therapy four of them in addition to permanent pacing Similarly we found that three of the four survivors in group 3 needed treatment with antiarrhythmic drugs and two permanent pacing as well

Parameswaran et al presented follow up infor mation covering periods of 10–30 months The main part of this information was provided by general practitioners Among their 17 patients they found continuous signs of SND in six one of whom be longed to the subgroup with sinus bradycardia and/or sinoatrial block At follow up we found signs of SND in 11 of 19 patients Only five patients showed symptoms which could be related to the arrhythmia

The detection of SND at follow up in nearly 60% of our patients in a one minute ECG is somewhat surprising As SND is often intermittently present this figure might be considered a minimum Patients with previously known SND were excluded from the study As regards patients with brady tachy syndrome there seems to be no doubt that the

arrhythmia appeared for the first time during the AMI In cases of sinus bradycardia/sinoatrial block the possibility of pre-existing (asymptomatic) SND cannot be completely ruled out This might be an explanation of the demonstration of SND in eight out of 15 patients at follow up However in a study of 128 patients with symptomatic SND (4) only two experienced an AMI during a mean observation period of three years Assuming a similar incidence of AMI in patients with asymptomatic SND it can be calculated that this population should be very large to contribute significantly to the present material Although the ratio asymptomatic/symptomatic cases of SND in the general population is unknown we assume that SND made its debut during AMI in patients in groups 1 and 2 as was the case regarding patients in group 3

The reported observation seems to indicate that SND appearing in AMI persists in a considerable number of patients In brady tachy syndrome treatment is most often necessary Symptoms accompanying other types of SND seem to b and inconstant and thus only occassionally treatment

ACKNOWLEDGEMENT

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REFERENCES

1 Parameswaran R Ohe T & Goldberg H node dysfunction in acute myocardial infar Heart J 38 93 1976
2 Rokseth R & Hatle L Sinus arrest in a ... dial infarction Br Heart J 33 639 1971
3 Rotman M Wagner G S & Walla e Bradyarrhythmias in acute myocardial infar culation 45 703 1972
4 Simonsen E Nielsen J S & Nielsen B I node dysfunction in 128 patients w th a follow- Med Scand 208 343 1980

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Blood Pressure Control in a Middle-Aged Male Population

A 6–9 Year Follow up with Special Reference to the Problem of Non Responders

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TRACT A health examination survey com ing 2322 men born in 1920–24 was carried out 970–73 at the University Hospital Uppsala eated subjects with a diastolic BP ≥105 mmHg those already on treatment for hypertension e considered hypertensives If a BP elevation was ied at a second screening and the patient had stablished contact with a physician he was ed treatment Thus 83 men have been followed or at least 6 years The overall reduction in SBP 6 years was 29 0 mmHg and in DBP 19 6 Hg Six men have died four of them from myo- al infarction five have dropped out for other ons The percentage of non responders (DBP≥105 Hg) 1 2 3 4 and 5 years ±3 months after the of treatment was high, about 20% on the age On the other hand, when the mean BP he non responders at all visits to the hyper on clinic was compared with their pretreatment e a reduction of 29.3 mmHg in SBP and 17 0 Hg in DBP was achieved The results with rd to compliance and BP reduction are en aging and would seem to justify more wide ad screening and treatment

words blood pressure control non responders lle aged men

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mmunity control of hypertension has been the ject of a special WHO report (10) In this report s considered inadvisable to start widespread ulation screening before successful pilot pro- mmes have been carried out The reason given he necessity for answering certain preliminary stions for example Is it possible to normalize blood pressure (BP) and to keep it normal in st people? Can symptom free hypertensives continue with life long treatment? What will be the psychological response to long term therapy in people without symptoms from their disorder?

This article deals with some of these problems on the basis of a programme aimed at bringing ele vated BP under control in middle aged men

STUDY POPULATION

All men living in the urban district of Uppsala and born in 1920–24 were invited to undergo a health examination between 1970 and 1973 A total of 2322 men were ex amined giving a participation rate of 83 9% (3)

Untreated subjects with a supine diastolic BP (DBP) ≥105 mmHg and those already on treatment for hyper tension were considered hypertensives There were 174 men who met these criteria If BP elevation i e supine DBP ≥105 mmHg was verified at a second screening examination at a special hypertension clinic (HT clinic) they were offered treatment at this clinic excluding 91 men with previously established contact with a physician Thus 83 men remained They have been continuously followed up for up to 9 years The results are given in this paper

METHODS

The BPs in the supine position after 10 min rest and in the erect position after 2 min of standing are recorded by a nurse at the HT clinic The DBP is read at dis- appearance of all sounds (Korotkoff phase V) and record ed to the nearest 5 mmHg mark

If possible the subjects were seen monthly until a sufficient BP reduction was achieved and thereafter at longer intervals always by the same physician (one of us) When the BP was well under control they were seen twice a year

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Abbreviations BP – blood pressure SBP = systolic BP DBP = diastolic BP HT clinic = hypertension clinic

Table I *BPs (mmHg) at the first screening and at the initial examination at the HT clinic (n 83) and annual progress during the following 6 years (n=72) (mean ± S D)*

	Supine		Standing	
	SBP	DBP	SBP	DBP
Screening	177 4±19 9	113 2± 8 0	174 1±21 1	117 6+ 9 4
Initial examination	177 5±24 2	113 3±11 2	174 8±24 6	119 4±1° 3
After				
1 y	150 9±19 9	97 7± 8 4	148 1±18 7	103 6± 8 0
2 y	147 7±17 5	96 4± 9 2	145 3±17 7	103 2± 7 1
3 y	145 5±19 8	94 3±10 1	144 7±20 4	101 2± 9 5
4 y	142 9±16 1	94 0± 9 2	141 7±15 6	100 1+ 8 8
5 y	147 1±17 3	94 0± 9 3	149 3±20 0	101 1±10 1
6 y	148 5±19 7	93 7± 9 2	146 9±19 4	100 6± 9 7

Propranolol (Inderal®) was given as the first drug to the previously untreated subjects The next step if necessary was to add hydralazine (Apresolin®) and the following if the BP was still not satisfactory to add diuretics

Conventional statistical methods were used in the analyses

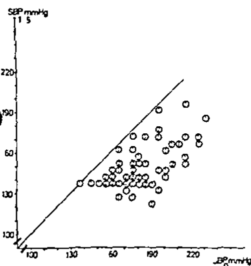
RESULTS AND COMMENTS

Blood pressure reduction

Table I gives the BPs at the first two screening examinations and the annual values for the remaining follow up period All have now passed the 6-year observation mark The DBP decreased gradually as did the systolic BP (SBP) during the first years whereafter a slight increase was seen After 6 years the average reduction of the supine SBP was 29 0 mmHg and of DBP 19 6 mmHg for whole group

The mean of all BPs during the 1-5-year p after commencement of therapy was calcu for each individual The relation between this m value and the pretreatment value is presen Fig 1 and the difference is the mean redu achieved for an individual subject (Fig 1). reason for excluding the BPs in the first year that treatment was instituted gradually during year

At each annual follow up—1 2 3 4 and 5 ±3 months after commencement of thera had not normalized (DBP <105 mmHg) in a ce number of men (Table II) These 39 non re pon



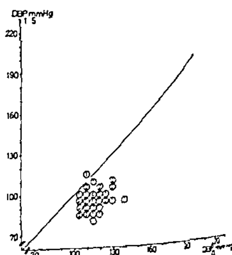
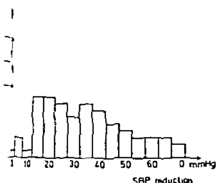
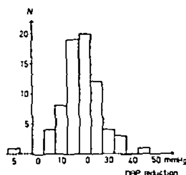


Fig 1 BP development over the years SBP DBP$_0$ – average of the two initial pressures SBP DBP$_{1-5}$ = average of the pressures at all visits to the HT clinic in the follow up period 1-5 years after initiation of treatment Figures in the circles indicate number of men with particular BP initially and during follow up





2 Number of individuals with a particular SBP and reduction The reduction comprises the difference een the average of the two initial SBPs and DBPs and the average of all SBPs and DBPs at the HT clinic 1–5 years after initiation of therapy

be referred to below as the failure group As in Table II a substantial percentage of the series was in this group However it is note hy that the composition of the failure group not identical from year to year On the other d when the mean of all BPs during the follow eriod was calculated for all individuals in the re group ($n=39$) it was found that the mean was on the average 21 9 mmHg below and rean DBP 12 9 mmHg below the pretreatment of the total group ($n=83$) In the failure p the mean SBP was 29 3 mmHg lower and nean DBP 17 0 mmHg lower in the follow up d than at the screening

e failure group is analysed further in Table III ils of 10 men appearing more than twice in 1-5 year period are given in Table IV A consid le average BP reduction occurred even in this group Several of those who did not reach a below 105 mmHg had had high initial BPs

ent adherence

re were 5 drop-outs during the 6–9 year follow period after 4 5 16 34 and 36 months Two of them had alcohol problems one preferred to visit his company doctor and two refused

Mortality and morbidity

Six men died four from myocardial infarction one from injuries after an accident and one committed suicide This man was depressed after an invalidating accident and there was no reason to suspect a drug induced depression No episodes of cerebrovascular lesion occurred during the follow up period

Antihypertensive medication

Table V shows the type of drugs used at present The single drug medication most commonly given is β adrenoceptor blocking agents Initially one purpose of the study was to evaluate the possibility of using β blockers to normalize the BP in a preventive trial like the present one Later the trend has rather been to add other drugs than to increase the dose of β blockers to a high level The number of men receiving combinations of β blocking agents and hydralazine and/or diuretics has therefore increased with time

ble II *Men with DBP ≥105 mmHg at annual low ups*

low up time	Non responders (%)
	28 4
	23 2
	21 3
	14 5
	20 3

Table III *Number of men appearing once or more in the failure group at 5 annual follow ups*

	No of non responders
Once	21
Twice	8
Three times	5
Four times	4
Five times	1

Table IV *Individual mean BPs at the two screening examinations and the mean of all BPs in the same subject in the failure group at 3–5 annual visits during the 5 year observation period*
Figures in parentheses indicate number of BP measurements

	Mean BP (mmHg)	
	At screening (×2)	Within 1–5 years
Three times	212 5/127 5[a]	192 2±22 7/108 4±10 5 (75)
	185/110	167 8±12 1/101 5± 8 0 (20)
	175/110	155 5± 8 1/100 8± 5 3 (19)
	165/112 5	147 3±11 9/102 3± 7 8 (15)
	177 5/117 5	155 6±12 9/102 5±11 0 (8)
Four times	192 5/112 5	166 5± 9 0/107 3± 8 7 (24)
	195/127 5 [b]	168 2±11 3/106 0± 8 8 (22)
	202 5/127 5	150 0±14 7/107 8± 8 6 (18)
	195/107 5[a,c]	190 0±26 0/115 0±13 0 (15)
Five times	222 5/130	175 3×12 3/106 8± 5 7 (20)

[a] Previously treated [b] Renovascular hypertension [c] Malignant hypertension and poor compliance to therap

In two cases it was necessary to withdraw the β blocking drug because of adverse effects namely bradycardia in one and weight gain in the other In another two cases the β blocker was withdrawn more or less for psychological reasons Another change during the present follow up has been the introduction of selective β blockers (atenolol and metoprolol) Thus in 11 subjects unselective β blockers were replaced by selective ones due to possible side effects suspected bronchial obstruction in five CNS related side effects in four and impotence in two cases Two further subjects in whom unselective β blockers had been considered contraindicated were given selective ones One subject developed symptoms of systemic lupus erythematosus with a positive antinuclear f while on hydralazine One man developed recu glycosuria while on a thiazide At the screen had a fairly low K value 1 05 in an i v glu tolerance test

Table V *Type of present medication (6–9 years after the start of therapy)*

	Per cent of all subjects (n=72)
Single drugs	
Adrenergic β-blocking agents	11 1
Diuretics	2 8
Combinations	
Adrenergic β blocking agents + hydralazine	29 2
Adrenergic β blocking agents + diuretics	26 4
Adrenergic β blocking agents + hydralazine + diuretics	19 4
Other drugs or combinations	11 1

DISCUSSION

This paper deals with some problems enco in an ongoing preventive trial aimed at contr hypertension in middle aged men All physic working in this field are well aware of the sp problems accompanied by preventive meas Most of the participants are asymptomatic i viduals with their own opinions sometimes v definite on the necessity of instituting ther or they may be very reluctant to accept care a suggested Another fact to be considered in handling of these subjects is the importance arranging their contacts with a physician with disturbing too much their ordinary daily life

The BP reductions over the years must be c ered acceptable in view of the special pr mentioned above The number of non respo varies considerably with the definition used Ap ing the definition supine DBP ≥105 mmHg number is high During the first 5 years about of the subjects fulfilled this criterion ea h y If a non responder is defined as a person sho a decrease in mean arterial pressure of less t 10% only two subjects who were examples of compliance would meet this criterion The responders as a group also showed a subs

ction of their BPs when measured over the ;e period (Tables III and IV) As pointed out ers (9) a partial reduction of BP should also cial Very few comparisons with the litera can be made as only short follow ups in simi eventive trials have previously been presented 7) The former two studies give results for o two years and the latter for up to one year r the periods that can be compared the BP ction is almost identical

op-outs during the 6–9 year period were few e of the long follow up and relatively fewer n other reported series (1 7 8) though the nt study population is smaller The good pa adherence must mean that middle aged men concerned about their health It should ressed that this group of subjects has been very leged in one respect All of them have met me doctor over the years which has been a ently repeated reason given by the subjects heir good compliance Other reasons might e easy accessibility of the treatment centre he fact that the HT clinic is open in the eve Although this is only a small scale experiment ventive medicine we feel encouraged by the duction and the good patient compliance to se more widespread community screening reatment programmes The outcome of such unity efforts is however dependent on good cian adherence to the programme and contin information about the benefit of decreasing BP This could be possible since hyper on is now well recognized as one of the most antial risk factors for the development of ovascular cerebrovascular and renovascular se (2 5 6)

conclusion the present study has shown that ajority of middle aged men with hypertension be treated in an acceptable way without too side effects and with a low drop-out rate The methods used to achieve these results are fairly simple requiring limited medical and economic resources

REFERENCES

1 Andersson O Berglund G Hansson L Sannerstedt R Sivertsson R Wikstrand J & Wilhelmsen L Organization and efficacy of an out patient hypertension clinic Acta Med Scand 203 391 1978
2 The Framingham Study An epidemiological investigation of cardiovascular disease Section 27 Coronary heart disease atherothrombotic brain infarction intermittent claudication—A multivariate analysis of some factors related to their incidence Framingham study 16-year follow up Government Printing Office Washington DC May 1971
3 Hedstrand H & Åberg H Treatment of hypertension in middle aged men A feasibility study in a community Acta Med Scand 199 281 1976
4 Henningsen N C Ohlsson O Mattiasson I Trell E Kristensson H & Hood B Hypertension levels of serum gamma glutamyl transpeptidase and degree of blood pressure control in middle aged males Acta Med Scand 207 245 1980
5 Lew E A High blood pressure other risk factors and longevity the insurance viewpoint Am J Med 55 281 1973
6 Schroll M & Hagerup L M Risk factors of myocardial infarction and death in men aged 50 at entry A ten year prospective study from the Glostrup population studies Dan Med Bull 24 252 1977
7 Stamler R Gosch F C Stamler J Ticho S Civinelli J Restivo B Pritchard D & Fine D Adherence and blood pressure response to hypertension treatment Lancet 2 1227 1975
8 Stamler J Stamler R Riedlinger W F Algera G & Roberts R H Hypertension screening of 1 million Americans Community Hypertension Evaluation Clinic (CHEC) Program 1973 through 1975 JAMA 235 2299 1976
9 Taguchi J & Freis E D Partial reduction of blood pressure and prevention of complications in hypertension N Engl J Med 291 329 1974
10 WHO Community control of hypertension Methodological considerations and protocol of a WHO cooperative project WHO Geneva 1973

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Emergency Treatment of Severe Hypertension Evaluated in a Randomized Study

Effect of Rest and Furosemide and a Randomized Evaluation of Chlorpromazine Dihydralazine and Diazoxide

Danish Multicenter Study

Organizing Committee

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ABSTRACT Emergency treatment of acute severe hypertension was monitored prospectively during a period of nine months in a Danish multicenter trial A total of 101 patients with supine diastolic blood pressure (DBP), phase V ≥135 mmHg in three measurements at 5 min intervals entered the study The emergency treatment was divided into three periods In period I lasting for the first hour, the patient was placed in the supine position and no drug treatment was given If DBP did not fall below 135 mmHg the patient entered period II during which furosemide, 40 mg i v was given and observation continued for another hour Patients with pronounced hypertensive encephalopathy ($n=15$) and left ventricular heart failure ($n=2$) started directly at period II Provided DBP thereafter was still 135 mmHg or higher the patients were randomized in period III (2nd–5th hour) to treatment with either chlorpromazine or dihydralazine in small refractory i v doses or diazoxide 5 mg/kg b wt i v, as a bolus injection In period I DBP fell below our "emergency limit" of 135 mmHg in 23 (27 %) of 84 patients whose mean arterial BP fell from 171 to 140 mmHg during the study In period II DBP fell below 135 mmHg in 23 (30 %) of 78 patients and their mean arterial BP decreased from 174 to 135 mmHg during the study In period III patients were treated with chlorpromazine 16 with dihydralazine and 15 with diazoxide In patients treated with chlorpromazine or dihydralazine BP decreased gradually during the first hour, on average from 211/146 to 155/103 and from 219/147 to 162/89 mmHg respectively After diazoxide BP decreased abruptly in the first two min to on average from 211/144 to 166/100 mmHg The complication rate was generally low and only a few patients were resistant to any of the treatments given The study was not able to demonstrate that diazoxide is preferable to the other two drugs in emergency treatment

Key words hypertension hypertensive encephalopathy treatment of hypertension chlorpromazine dihydralazine diazoxide

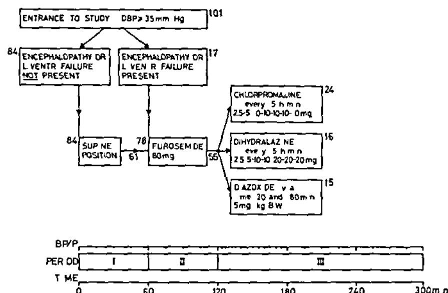
Acta Med Scand 208 473 1980

In recent decades several drugs have been recommended in emergency treatment of severe hypertension (1 5 6 10 15 16) As the annual number of patients requiring emergency treatment is low for a single medical department personal experience of such patients is often limited These factors seem to explain the considerable variations in the recommended treatment from centre to centre

Several reports have been published especially from the US (1 4 6 7 8 9 11 13 15 17 18 20

Collaborating doctors O Amtorp M Brøns J Bukh C K Christensen P Christiansen T Cortsen J Fischer Hansen M Friedberg R Friedberg K Garde E Geday K Ginger Mortensen L Hagerup J Hansen M Hilden G Hvid H Ærenlund Jensen P Jest P W Jørgensen J Kampmann B Østergaard Kristensen O Krogsøe J Ladefoged A Leth J Lindskov C Vind Ludvigsen I Madsen H Mørch P P Olsen G Pedersen K E Petersen H Overgaard Petersen V Rasmussen J Rokkedal K Sloth E Taudorf F Trautner H Winzentsen

Abbreviations BP = blood pressure DBP = diastolic BP SBP = systolic BP



F g 1 Des gn of the s ud

22) which recommend administrat on of the vasodi lating drug diazoxide in emergency treatment of se vere hypertension In only one controlled trial (2) on hypertensive subjects with only slightly elevated blood pressure (BP) has diazoxide so far been compared to other drugs trimethaphan and sodium nitroprusside in emergency treatment We there fore decided to perform a multicenter trial compar ing diazoxide to dihydralazine and chlorpromazine in the treatment of severe hypertension Dihyd ralazine has for several years been a well known drug in emergency antihypertensive therapy and chlorpromazine has been used for years in many medical wards in Scandinavia with satisfactory re sults

This report deals with experiences of the first part of the multicenter trial comprising about 100 pat ents

STUDY BASE AND METHOD

The study was performed between Jan 10 1977 and June 1 1978 Thirty n ne med cal departments const tut ng 43% of all med cal beds in Denmark (5 m ll inhab tants) jo ned the study *Posit e ncl is on cr ter on* average sup ne diastol c blood pressure (DBP) ≥135 mmHg in three consecutive measurements at 5 m n intervals *Nega t e incl s on cr teria a)* Severe ischaemic heart disease (history of myocard al infarct on severe angina pectoris) *b)* Uraemia with S-creat n ne above 500 µmol/l *c)* Earlier or recent cerebrovascular attack (thrombosis haemor rhage subarachno dal haemorrhage trans tory chaem c attack)

Tl e a sci ltator meas rements were performed us ng standard cuffs (12×35 cm) or for pat ents w h arm circ ference over 35 cm 14×45 cm cuffs (23) DBP was corded at disappearance of Korotkoff sounds phase

The study co ered the first five hours d ded three periods (F g 1)

Per ods I and II Dur ng the first hour period I patients were n the sup ne pos t on Patie s symptoms of severe hypertensive encephalopathy or se vere left ventricular heart failure however entered study at period II If DBP at 45 and 60 m n a mmHg or more the pat ent cont nued to period II and mg furosem de was njected ntravenously If DBP lower than 135 mmHg the pat ent remained emergency study and BP and heart rate were measured every half hour for the follow ng 4 hours During period wh ch lasted one hour the same l m ts of BP were used dec de whether the pat ent should cont nue to period

Per od III The rema n ng pat ents were allocated treatment with either chlorpromazine d hyd d azox de Closed envelopes numbered conse and stat st cal tables of random zed numbers were used

The recommended and max mum doses of the drugs are l sted n Table I Chlorpromazine and ralazine were g ven as small bolus nject ons e until DBP had fallen to 110 mmHg or below po nted out n the protocol that f the BP fell rap prev ous nject on the next do e of the drug reduced in order to a o d se ere hypotension was given n the recommended dose 5 mg/kg b injected i v in runn ng drip o er 0-30 sec If the BP not suff c ently reduced (DBP>110 mmHg) a new t on of diazoxide could be given one hour later For pat ents allocated to treatment w th d azoxide a drip metaradrine (Aram n®) should be prepared The hypertensive treatment after the study was not uled in the protocol

Any side-effects of the treatments were described reports as well as nformat on about known hypertens before the study and an evaluation concern ng sympto

el D s s f cll rpr c e ll lr l t c d d t x de l stere l per d III
so of pa en s g ven the recommended dose

	M nutes							Maximum recommended dose during the f rst 1 ½ h n period III	Doses used n the study	
	0	15	30	45	60	75	90		Mean	Range
lorpromaz ne (mg)	7 5	5	10	10	10	10	10	57 5	25 3	7 5–67 5
	4	4	17	9	7	5	?			
hdralaz ne (mg)	7 5	5	10	10	0	0	0	87 5	16 5	7 5–47 5
	16	14	9	4	1	0	0			
de (mg/kg b wt)	5				5			2×5	360	90–600
	15									

se sen al hypertens on S-creat n ne was measured re and on the day after the study ECG and the ret nal s were e aluated at entrance to the study as we e oms cons stent w th hypertens e encephalopathy

ien s A total of 103 pa ents were n t ally ncluded udy Two pat ents were excluded secondarily one subcutaneously adm n stered d hydralaz ne and the due to l doca ne nfus on Data on the remain ng 101 s are given n Tables II and III The male/female was approx ma ely 1 The age of the pat ents aried l to 8 years the a erage age of those who stopped ods I and II was sl ghtly h gher than that of the ts who cont nued to period III Only 44 of the pa had known hypertens on befo e he study The on of ant hypertens e treatment varied among pat ents from 2 weeks up to 32 years A total of ? s had secondary hypertens on (Table II)

mptoms cons stent w th hypertensive encepha hy at entrance to the study (i e confus on muzzi somnolence coma nausea vom t ng headache s convuls ons v sual d sturbances paraesthes a) found n 44 pat ents (Table III) In 15 cases these ptoms were so pronounced that the pat ent entered tudy at period II Only two pat ents started at period II on account of left ventricular heart failure ECG abnor mal t es (left ax s dev at on left ventricular hypertrophy and/or left ven ricular strain) were demonstrated n 81 pat ents In only four pa ents were the ret nal vessels described as normal Forty pat ents had se ere ret nal changes w h fundus hyperton cus III and IV accord ng to he Ke th Wagener grad ng The a erage S-creat n ne varied n these f ve groups of pa ents from 110 to 160 µmol/l (Table III)

E l cal co s de a o s During the plann ng of the study the e h cal problems n ol ed we e carefully d scussed Because three well establ shed treatments were given we found that the s udy fulf lled the criteria of Hels nk decla rat on II

S at t cal tests Student s *t* test for unpaired observa t ons W lcoxon matched pairs s gned rank test and χ^2 test w th Yate s correct on were used

RESULTS

Cl ges blood press re

P t ents t cont g to per od III In 46 patients DBP decreased below the emergency l m t (135

le II Age d sex d st b t nd f rmat o abo t l ypertens on

	No of pats			Age (y)		Known hypertens on on adm ssion				Symptomat c hypertens on	
								Durat on of ant hypertens ve treatment (y)			
	Total	♀	♂	Mean	Range	No	% of total	Mean	Range	No	% of total
od I	3	11	12	5 1	4–74	1	5	6 ?	<1 3	1	4
od II	23	11	12	57 7	32–87	13	57	5 9	<1 0	6	6
od III											
hlorpromazine	4	12	12	50 0	36–70	7	9	3 6	<1 10	5	1
hydralazine	16	6	10	47 0	5–65	6	38	1 5	<1–4	3	19
azox de	15	7	8	46 8	1 71	6	40	9 1	<1 3	7	47
al	101	47	54	51 8	1–87	44	43 6	5 4	<1 3	?	?1 8

Table III *Hypertensive organ damage at entrance to the study*

	Total no of pats	Hypertensive encephalopathy		Pats entering at period II		ECG abnormalities		Retinal fundus Keith Wagener 0→II		III+IV
		No	%	No	%	No	%	No	%	No
Period I	23	9	39			18	78	19	83	4
Period II	23	8	35	4	17	16	70	17	74	6
Period III										
Chlorpromazine	24	14	58	5	21	22	92	11	46	13
Dihydralazine	16	8	50	4	25	13	81	4	25	1?
Diazoxide	15	5	33	2	13	12	80	10	67	5
Total	101	44	43 6	15	14 9	81	80 2	61	60 4	40

mmHg) during period I (23 patients out of 84=27%) or period II (23 out of 78 = 30%) (Fig 2) A further decrease in BP was observed during the next hours At the end of the study average BP was almost the same in the two groups 190/115 and 177/113 mmHg compared to 225/144 and 236/143 mmHg respectively at entrance Thus the decrease in mean BP during the 5 hours of observation was 37 and 40 mmHg respectively in the two groups

Patients continuing to period III Fifty five patients were allocated to treatment with either chlorpromazine (24) didhydralazine (16) or diazoxide (15) (Fig 3) BP decreased gradually with chlorpromazine and dihydralazine during the first hour of period III with no significant difference between the two groups (Table IV) The individual doses of the two drugs varied considerably (Table I) the average dose of chlorpromazine being 25 3 mg

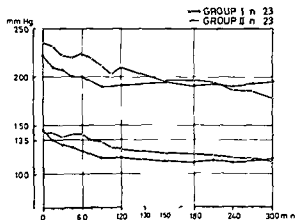


Fig 2 Changes in SBP and DBP in patients responding to treatment with supine position alone (group I) or supine position + furosemide (group II)

(range 7 5–57 5) and of dihydralazine 16 5 mg (r 2 5–47 5) The maximum recommended dos chlorpromazine was given to only two pati while none of the patients received the maxi recommended dose of dihydralazine In 27 of th patients in these two groups BP was already l ered sufficiently after the first three injections

In the group treated with diazoxide (Fig 3 T IV) an immediate drop in BP was observed on min after the injection (from 218/144 to 166 mmHg) during the next hour it increased sl Only two patients received an injection of diazo one hour after the initial injection The average 3 4 and 5 hours after entrance to the study sho no statistically significant differences between three groups of patients treated during perio (Table IV)

The individual responses to emergency treat varied considerably After the initial 90 m period III 37 of the 55 patients had a DBP of mmHg or below (Fig 4) Four patients still DBPs above the "emergency limit" (≥135 mm three in the chlorpromazine and one in the d ralazine treated group while none of the oxide treated patients had BPs above this limit

Severe pressure drop (systolic BP (SBP) mmHg) was observed in 12 patients (4 in the c promazine 2 in the dihydralazine 6 in diazoxide group) (Table V) The differen e tween the three goups are not statistically si cant In 2 of the patients treated with c promazine the fall in BP seemed to be expla vasovagal attacks as the heart rate decreased siderably

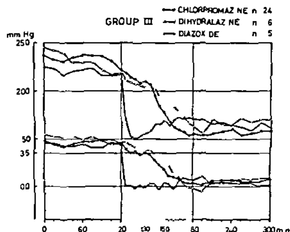
Secondary pressure rise later during the ho

c µmol			
e	4 h after he s udy		
Range	Mean	Range	
88–305	140	88–305	
70–3 4	1?7*	63– 18	
0–3 4	152*	70–3?3	
0– 90	141	65– 90	
84–36	184	85–394	
0–362	146 4	63–394	

w th DBP ncreas ng to 135 mmHg or more he n t al emergency study was demonstrated of the 46 pat ents who left the study dur ng d I or II and n ?6 of the 55 who cont nued to ment n period III (χ^2 3 8 $p<0$ 01)

nges l e rt r te

gn f cant ncrease n heart rate was found ng the pat ents treated w th d hydralaz ne e only a small non s gn f cant ncrease was d among those g en d azox de or chlor maz ne Severe tachycard a w th heart rate e 140 was observed n two pat ents treated w th dralaz ne (Table V) The two pat ents who de ped bradycard a due to vasovagal attacks dur hlorpromaz ne therapy were treated succesful h atrop ne



F g 3 Changes n SBP and DBP n pa ents alloca ed to treatment during period III

Co pl cat o s and s de effects

The nc dence of early compl cat ons and s de ef fects is g ven n Table V No compl cat ons were seen n the 46 pat ents who left the emergency study during period I or II The 1? pat ents w th severe p essure drop during per od III have already been ment oned E ght pat ents compla ned of nausea vom t ng and abdom nal pa n dur ng period III No card ac compl cat ons were observed apart from precord al pa n n two pat ents treated w th d hyd ralaz ne A 53 year old man developed a hem paresis dur ng treatment w th d hydralaz ne n the f rst hour of period III H s BP decreased stead ly during this hour from ?50/1?0 to 120/80 mmHg Wh le st ll n hosp tal he obta ned remiss on of the

e IV *Blood press re (n Hg) eas red d r g per od III (ean + S D and range (n pa entl eses))*

men group	1 0 m n	160 m n	40 m n	300 m n
orp omaz ne (*n* 24				
BP	1+ 6	155+40	160 3	158 9
	(160–270)	(100– 0	(110– 0	(1 0– 5)
BP	146 9	103	107 18	108 17
	(130–160	(70–145)	(80–145)	(80–140
hydralaz ne (*n* = 16				
BP	19 1	163 31	165 31	170+33
	(180–250)	(105– 00)	(90– 10)	(110– 3)
BP	147 11	98 18	105 19	08 18
	(130–170	(95 1 5	65 1 0)	(80–130
ox de (*n* 15				
P	18 3	171 37	165 31	153 43
	(175– 85)	(110– 0)	(110– 30)	(100– 0
BP	144 10	107 14	104 15	10 18
	(130–170	(85–130	85 140	(75–135)

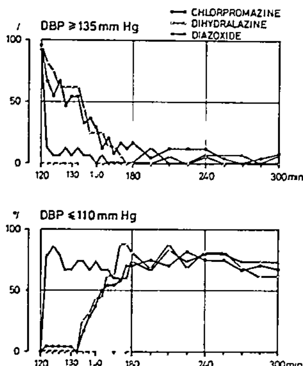


Fig 4 Percentage of patients with DBP ≥135 or ≤110 mmHg during period III

hemiparesis but at discharge a slight paresis was still demonstrable Cerebral arteriography was not performed In a 50-year-old woman arm paresis and paresis of the facial nerve on admission deteriorated during treatment with chlorpromazine followed by remission Her BP decreased from 245/155 to 95/80 mmHg during the first 45 min in period III The total dose of chlorpromazine administered to this patient was only 7 5 mg

Changes in renal function

A significant increase in S-creatinine was observed in all five groups during the first 24 hours (Table III)

Late complications

Six patients died later during the hospital ... four primarily due to intracerebral haemorrha... cerebral oedema and one patient each of my... dial infarction and severe uraemia. One patie... veloped secondarily severe encephalopathy subarachnoidal haemorrhage followed by ... ate remission

DISCUSSION

In the present study a DBP level of ≥135 ... was used as indication for emergency treat... Such a rigid limit is of course debatable espe... as many of the patients were not affected by ... high BPs On the other hand a multicenter ... requires a protocol that is not too differen...

This study was initiated in order to answer the following three questions 1) How often can se... ly elevated BP be treated by just placing the p... in the supine position possibly followed by ... furosemide? 2) If further treatment is ne... how efficient is chlorpromazine dihydralazin... diazoxide? 3) Is it possible on the basis of the ... to decide which of these drugs should be pref... in emergency therapy?

The study showed that about one fourth of ... patients reached a clinically acceptable BP ... by being placed in the supine position for one h... A further one fourth reached an acceptable BP ... i v furosemide In none of these patients ... complications recorded during the emergency ... or later during the hospital stay

Compared with group III the patients in gro... and II included a significantly lower pro... with pronounced retinopathy (Table III) ... a less severe form of hypertension Earlier ... hypertension was also more frequent in gr... and II than in group III

Table V *Complications and side effects during the study*

	Total no of pats	No of complications and side-effects SBP ≤100 mmHg	Nausea vomiting sweating	Pre cordial pain	Tachy cardia ≥140	Brady cardia <50	Hemiparesis	T...
Periods I and II	46							
Period III								7
Chlorpromazine	24	4	2			2		9
Dihydralazine	16	2	3	2	2		1	[illegible]
Diazoxide	15	6	3					

d three emergency treatments used in the pres sudy were effective in lowering the markedly sed BP as only few of the 55 patients could be racterized as non responders The hypotensive ct of dihydralazine and diazoxide is well known many clinicians outside the Scandinavian coun are probably not aware that the α blocking ct of chlorpromazine (21) is useful in hyperten emergency Comparison of the three drugs ned a slow and quite similar decrease in BP in groups treated with dihydralazine and chlor mazine respectively In contrast diazoxide (5 kg b wt) was followed by an immediate fall in on average 2 min after the i v injection cor rding to the findings of several other authors 7 12 13 17 18 20 22)

his immediate effect of diazoxide followed by stently lowered BP for the next hours gives e advantages compared to the repeated bolus tions of chlorpromazine and dihydralazine On other hand repeated injections of the other two s yield valuable information about the sensitivi f the patient (Table I) Some clinicians have ted that repeated injections are time-consum However the present study showed that using recommended dose of chlorpromazine or dihyd ine about 2/3 of the patients (27 of 40) reached mmHg in DBP after only three injections given ervals of 15 min

e number of patients in the present study is too to show whether one of the three drugs is rable to the others in terms of a lower compli n rate As a whole the complication rate was ry low The vasovagal attacks were found ng patients treated with chlorpromazine but rding to the literature this has also been found ng patients treated with diazoxide as well as dralazine (14 19) The patient who developed a paresis during period III may have had an int pressure rise after an intracerebral attack ever the other possibility exists that adminis on of dihydralazine increased the intracerebral ssure with a secondary decrease in intracere l flow as recently shown in patients with trau c head injuries (24)

hypertensive encephalopathy is probably ex ted by a break through phenomenon i e the bral blood flow is constant over a wide range of but at a very high sustained pressure cerebral d flow will increase followed by cerebral ema It is not yet known whether it is preferable to reduce the BP slowly or rapidly The autoregula tion of the cerebral vessels is probably able to coun teract even rapid changes in BP such as were seen in patients treated with diazoxide (12) The lower limit of the autoregulation curve seems to be shifted to higher levels among hypertensive than nor motensive subjects (26) i e symptoms consistent with cerebral anoxia might be demonstrated at higher BP levels among the former Severe hypotension should therefore be avoided during emergency treatment No symptoms of cerebral anoxia were noted among our 12 patients who de veloped hypotension during period III (SBP≤100 mmHg) On the other hand a sudden severe reduc tion of SBP might be potentially dangerous not only to the cerebral circulation but also to the myocardial and renal circulation (14) So far no comparisons of cerebral haemodynamics have been performed using different emergency treatments in severe hypertension (26)

Diazoxide is often recommended in the Anglo-Saxon literature as the drug of first choice in emer gency therapy due to its immediate and long acting effect very low incidence of complications and side effects and very low failure rate (1 5 8 9 21) This recommendation seems to be based on clinical ex perience not on controlled trials In the present study chlorpromazine and dihydralazine were both quite as effective as diazoxide in lowering the BP Furthermore it is fair to conclude from this study that the recommended dose of diazoxide (5 mg/kg b wt) is too high for a rather large group of the patients It has been shown in hypertensive children (3) that diazoxide might be given as smaller i v bolus injections (1–2 mg/kg b wt) repeated every 10–15 min Recently Ram and Kaplan (25) found individual titration of diazoxide 150 mg every 5 min effective in controlling severe hypertension Our preliminary results agree with the results of their study

ADDENDUM

When we had finished this part of the study two British groups reported on 12 patients with severe neurological complications or even fatal cases after hypertensive emergency therapy (Cove et al Br Med J II 245 1979 Ledingham & Rajagopalan Q J Med 48 25 1979) The publications have been dis-cussed extensively in leading articles in Br Med J and the Lancet The case reports showed that rapid

reduction of high BP might be dangerous especially if hypotension or even normotension is achieved In our opinion the majority of the patients had been overtreated whether using diazoxide in a large i v bolus injection or diazoxide combined with phenothiazine derivates such as chlorpromazine However one of the patients developed irreversible blindness even after only peroral medication with a slow reduction of BP over three days

It seems important to stress that emergency therapy might be dangerous and that the BP should be lowered steadily and not to normotensive values within the first days after initiation of the therapy

REFERENCES

1 AMA Committee on Hypertension The treatment of malignant hypertension and hypertensive emergencies JAMA 228 1973 1974
2 Bhatia, S K & Frohlich E D Hemodynamic comparison of agents useful in hypertensive emergencies Am Heart J 85 367 1973
3 Boerth E C & Long W R Dose–response relation of diazoxide in children with hypertension Circulation 56 1062 1977
4 Broch Møller R. & Kølendorf K Diazoxide in the management of severe hypertension Acta Med Scand 198 385 1975
5 Curry C L & Hosten A O Current treatment of malignant hypertension JAMA 232 1367 1970
6 Diazoxide A review of its pharmacological properties and therapeutic use in hypertensive crises Drugs 2 78 1971
7 Edwards J C Use of diazoxide for refractory hypertension Missouri Med 498 1974
8 Finnerty F A Hypertensive encephalopathy Am Heart J 75 559 1968
9 Finnerty F A Jr Kakaviatos N Tuckman J & Magill J Clinical evaluation of diazoxide A new treatment for acute hypertension Circulation 28 203 1963
10 Freis E D Hypertensive crises JAMA 208 338 1969
11 Garde K & Krogsgaard A Diazoxidum—et blod trykssnedsættende tiaziddenvat uden diuretisk v ning. Nord Med 71 7-6 1964
12 Goldberg H I Codano R. A Barka, R Reivich M Patterns of cerebral dysautoregula severe hypertension to blood pressure reduction diazoxide Acta Neurol Scand (Suppl) 64 64 19
13 Hamby W M Jankowski G J & Pouget J Intravenous use of diazoxide in treatment of v hypertension Circulation 37 169 1968
14 Henrich W L Cronin R Miller P D & A sen R J Hypotensive sequelae of diazoxide hydralazine therapy JAMA 237 264 1977
15 Keith III T A Hypertension crises Recog. and management JAMA 237 1570 1977
16 Koch Weser J Vasodilator drugs in the treatm hypertension Arch Intern Med 133 1017 1974
17 McDonald W J Smith G Woods J W H M & Danielson B D Intravenous dia therapy in hypertensive crises Am J C 1977
18 Miller W E Gifford R. W Humphrey D Vidt D G Management of severe hy intravenous injections of diazoxide Am J C 24 870 1969
19 Mizroch S & Yurasek M Hypotension bradycardia following diazoxide and hydra therapy JAMA 237 2471 1977
20 Moser M Diazoxide—an effective vasodilator celerated hypertension Am Heart J 87 791 1974
21 Moyer J H Morris G Pontius R & Henstlee R Effect of chlorpromazine on cerebral modynamics and cerebral oxygen man Circulation 14 380 1956
22 Mroczek W J Davidov M Gavrilovich L & nerty F A The value of aggressive therapy in hypertensive patient with azotemia. C 40 893 1969
23 Nielsen P E & Janniche H The accuracy of cultatory measurement of arm blood pressure in obese subjects Acta Med Scand 195 403 1974
24 Overgaard J & Skinhøj E A paradoxical cer hemodynamic effect of hydralazine Stroke 6 1975
25 Ram C V S & Kaplan N M Individual tu of diazoxide dosage in the treatment of severe hy tension Am J Cardiol 43 627 1979
26 Strandgaard S Autoregulation of cerebral cir tion in hypertension Acta Neurol Scand (Sup 1978

Acta Med Scand 208 481–489 1980

Borderlıne Hypertensıon

Hypertension Seminars at Ostra Hospital Goteborg Sweden

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:ACT Borderline hypertension was the topic of the Hypertension seminars" arranged by pertension Section at the Ostra Hospital rg, Sweden On that occasion Professor Stevo Ann Arbor Michigan, USA, was an invited During the seminar, various aspects of border were discussed, e g the natural his- emodynamics and management of this condi he present review is based on these discus

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been shown beyond doubt and there is gen reement today that arterial pressure in any tion is distributed as a continuous variable ves being Gaussian in shape when converted logarithmic scale In other words arterial e is a quantity not a quality With this in t is not logical to treat arterial pressure as a and set up a dichotomy normotension and ension a fact repeatedly pointed out by Sir Pickering (75 76)

fact that most physicians and scientists still e terms hypertension and normotension and e term borderline hypertension the topic of minar does not mean that they do not recog at blood pressure (BP) is a quantitative vari The use of these terms reflects the realization ndividuals with a certain level of BP have l common physiologic and epidemiologic cteristics which often mandate specific inves e and practical approaches As will become it during this seminar the term borderline tension signifies not just a certain range of BP en normotension and hypertension but rather a clinical condition with recognizable and reproducible characteristics

DEFINITIONS

The WHO has defined hypertension as systolic BP (SBP) ≥160 and/or diastolic BP (DBP)≥95 mmHg and normotension as ≤140/90 mmHg leaving the range between these two delineations to be called borderline hypertension (101) The Ann Arbor group has previously defined patients with borderline hypertension as those having out of five indirect casual BPs within the last year at least one with a diastolic value ≥90 mmHg and at least one ≤90 mmHg (45) Others have defined borderline hypertension as BP intermittently above 150 mmHg systolic or 90 mmHg diastolic (94) Since arterial pressure tends to increase with age in the Western world all the above definitions have inherent problems simply because they do not consider the age of the subject However the Ann Arbor group has recently taken age into consideration and defines borderline hypertension in the following manner age 17–40 >140/90 <160/100 age 41–60 >150/90 <160/100 and age >60 >160/90 <175/100 (40) Obviously the intent of all these classifications is to delineate the mildest possible form of hypertension Consequently the term borderline hypertension excludes the existence of BP related target organ damage such as hypertensive retinopathy and left ventricular hypertrophy (with conventional methods) or impaired renal function

A number of synonyms to borderline hypertension have been proposed The term labile hypertension is not logical as it implies increased BP variability Some of the early studies indicating a higher degree of BP variability in subjects with systolic blood pressure above 120 mmHg as compared to those with BPs below this level are open to serious criticism e g that in the lower BP group the upward variability of the BP was limited by definition (it could reach a maximum of 120 mmHg) whereas no such restrictions existed in the high BP group (78)

Furthermore several studies have demonstrated that there is no correlation between the level of BP and its variability when repeated measurements are made during 1–3 weeks (10 26) In addition BP fluctuates markedly

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even in normotensive individuals (4) It is therefore not surprising to find that an excessive variability of BP has never been established as a characteristic feature of borderline hypertension Even if the BP variability were increased the importance of this finding would be questionable The extreme ranges of BP do not seem to predict the risk of cardiovascular disease Thus Sokolow et al (85) found that the five highest and five lowest BPs during a 24-hour recording did not relate to cardiovascular morbidity whereas the average BP during that period carried an important predictive power The term labile should be reserved for individuals with extremely variable BPs irrespective of whether these occur in the normotensive borderline or hypertensive range

The term prehypertension indicates a condition which almost invariably leads to established hypertension Since this is not the case which will be shown later the term is not logical Latent hypertension points to a condition which may develop into hypertension or which may remain latent and this term is accordingly a useful synonym Marginal hypertension is also acceptable whereas early essential hypertension should be avoided for the same reasons as prehypertension However borderline hypertension is such an accepted and commonly used expression that any attempt to use synonyms for this condition is likely to cause confusion For this reason we would recommend that the use of synonyms be restricted

EPIDEMIOLOGY

The prevalence of borderline hypertension has been studied in several population surveys In the Bergen study performed in the 1950s 8% of the males in the age group 20–30 years had borderline hypertension and 13% in the 30–40 years group The prevalence of borderline hypertension was somewhat lower in women below 50 years of age but with increasing age this difference disappeared (6) Also in the US the prevalence of borderline hypertension increases rapidly with increasing age (7) The prevalence of borderline hypertension in university students in Michigan has been reported to be approximately 20% (40)

Accurate data about the prevalence of borderline hypertension in Sweden are lacking However if the prevalence data from the Alameda County BP study in California were valid also in Sweden the total number of persons with borderline hypertension would exceed one million (of a total population of 8 millions) (Table I)

For a complete review of available data on the prevalence of borderline hypertension see Julius and Schork (47) In this context it should be stressed again that the definition of borderline hypertension and indeed also of hypertension becomes crucial with advancing age For example a

Table I *Calculated number of persons with borderline hypertension in Sweden*

Based on population data on Dec 31 19 6 the population of Sweden being 8236179 (90) and Alameda County BP study (7)

Age group	Males	Females
18–24	19 900	7 600
25–44	114 200	54 400
45–64	163 100	196 700
>65	106 800	357 400
All	403 800	616 000
All males and females	1 019 800	

population study of 70-year old women in G[illegible] indicated that no less than 48% had hyperten[illegible] (92) demonstrating the dilemma of arbitrary [illegible]finitions of hypertension The incidence of bor[illegible]line hypertension has repeatedly been found to [illegible] quite low in the order of 1%/year of observa[illegible] (47 52)

NATURAL HISTORY AND RISK FACTOR[illegible]

The later occurrence of established hyperten[illegible] has repeatedly been found to be 2–5 times [illegible] common in individuals with borderline hyper[illegible]sion than in those with initial normal BP [illegible] should be stressed that only a minority of indi[illegible]als with borderline hypertension later develo[illegible] tablished hypertension An approximate fig[illegible] the accumulated overall risk is commonly [illegible]sidered to be around 20% (44 70 73)

The morbidity and mortality from cardiovas[illegible] disease in the population with borderline hyper[illegible]sion is approximately twice as high as in a [illegible]motensive population (47) The increased mor[illegible] in borderline hypertension shows a similar pa[illegible] to the morbidity observed in established hyper[illegible]sion Thus an excess in myocardial infar[illegible]sion strokes congestive heart failure and ECG cha[illegible] has been reported (32 51 57 62 68 96) [illegible]sequently it is likely but not proven that th[illegible] er morbidity occurs in the group (20%) of p[illegible] who will later develop established hyperte[illegible] (hypertension specific cardiovascular morbid[illegible]

A good example of morbidity in borderline hy[illegible]tension can be found in the Framingham s[illegible] which showed a 50% increase in age adjusted c[illegible]nary heart disease (50 51) Other studies [illegible] shown similar or higher (up to 200%) increase

...ary morbidity in borderline hypertension (39 ...) The Framingham study also found an al... doubled incidence of atherothrombotic brain ...tion

The mortality in borderline hypertension is also ...eased One could question the specificity of this ...ality since in the report by Levy et al (57) ...nts with borderline hypertension had a greater ...dency to commit suicide However the Framing... study shows that the excess mortality in ...rline hypertension is specific ...50% increased overall mortality for men and a ...% increase for women with borderline hyperten... as compared to normotensive control groups ... reported The increase is largely due to car...vascular mortality which was twice the normal ... for men and four times that for women in age ...p 67–74 (50) In younger age groups the in...ase in cardiovascular mortality was substantial ...not as dramatic as in older ages (50)

As the risks for complications increase with rising ...(65) it is not surprising that a great deal of work ... interest have gone into attempts to identify ...tors that predict future hypertension As it hap...s the best predictor for future hypertension is ...BP i e the initial level is the strongest predic... for BP in the future (11 32 48 64 69 87) ...ther independent predictive factor is tachy...dia which is *not* a benign sign (70 87) Levy et ... found that when both transient hypertension and ...sient tachycardia were present the incidence of ... established hypertension was more than twice ... incidence when only one of these factors was ...sent (58)

Overweight is also associated with borderline and ...ld hypertension High relative weight is a predic... of future hypertension as is weight gain over a ...riod of years (32 37 38 70 87 89)

A positive family history of hypertension is more ...mmon in patients with borderline BP elevation ...) and established hypertension occurs more of... in patients with a positive family history (29) ...e inheritance of arterial pressure is considered to ... multigenetic but the exact mechanisms are not ...ll known (80 97)

Interest has recently been focused on possible ...teractions between environmental and genetic ...munological factors in the development of hyper...sion (12 93) The question has been asked ...hether there are genetic indicators—e g certain ...LA types—at least in some subpopulations in es...sential hypertension If so it might be possible to predict the prognosis or the risk for e g vascular damage more reliably than is presently possible (27 53) However to our knowledge no such studies have been performed systematically in individuals with borderline hypertension

In the overall US population the prevalence of borderline hypertension is very similar for black and white persons of both sexes but established hypertension is twice as frequent in blacks indicating that race may be considered as a risk factor and that blacks carry a greater risk for progression from borderline to sustained hypertension (40)

Using multiple logistic function to discern the quintile of the population with the highest risk of developing hypertension within 5 years Stamler et al (87) could identify at most 55% of all expected hypertensives in that quintile

A number of tests have been designed and employed in attempts to identify persons with an augmented risk of developing future hypertension e g cold pressor test salt loading reaction to mental arithmetic digital vascular reactivity to noradrenalin apparent noradrenalin secretion test and tritiated noradrenalin test as well as different combinations of these By and large such tests have proved to be of no predictive value or alternatively they cannot be employed in practice or the needed long term follow up is still lacking (40 91) This holds true also for a new and most interesting approach the abnormal Na+ and K+ net fluxes in erythrocytes of essential hypertensive patients (also in relatives to hypertensive patients and in some women with hypertension during pregnancy) (25) Whether these abnormalities can really be used as markers for hypertension remains to be confirmed

HUMORAL FACTORS

Catecholamine concentrations in urine or plasma are frequently used as indicators of sympathetic activity It is however doubtful that patients with established hypertension have increased sympathetic activity as reflected by increased release of catecholamines (8 15 18 19 23 34 55 59 68 74 81) Age is of importance in this setting since plasma concentration of noradrenalin is positively correlated with age (23 34 74 81) Activation of the cardiac sympathetic neurones increases urinary catecholamine excretion (9) whereas moderate activation of the peripheral sympathetic ner...

Acr

Table II *Hemodynamics in borderline hypertension*

	Controls (*n*=29)	Whole patient group (*n*=44)	Hyperkinetic subgroup (*n*=20)	Normokinetic subgroup (*n*=24)
Blood pressure (mmHg)				
SBP	120	137***	138 *	136*
DBP	71	75**	76 *	74
Mean	88	95***	97 *	94
Heart rate (beats/min)	65	69	76* *	Δ 65
Stroke volume (ml)	98	111**	119 *	Δ 104
Cardiac output (l/min)	6 1	7 3***	8 6***	ΔΔΔ 6 ?
Cardiac index (l/min m²)	3 33	3 81*	4 55**	ΔΔΔ 3 19
Total peripheral resistance (mmHg/l/min)	14 8	13 4*	11 2**	ΔΔΔ 15 ?
Minimal vascular resistance in the hands (mmHg/(ml/min 100 ml))	1 69	1 87*	1 71	Δ 1 9?
Body weight (kg)	65 9	73 8***	71 4*	75 ?

* $p<0\ 05$ ** $p<0\ 01$ *** $p<0\ 001$ in comparison with controls Δ $p<0\ 05$ ΔΔ $p<0\ 01$ ΔΔΔ $p<0\ 001$ in comp[...] with hyperkinetic subgroup (Sivertsson et al Unpublished data)

system does not increase plasma concentrations of adrenalin or noradrenalin (1 61) Some patients with established hypertension appear to have a true neurogenic hypertension and their BP can be normalized following total autonomic blockade (16) Hypertensive patients showing higher noradrenalin levels are usually young (23 34 81) and have also been reported to have increased plasma renin activity (16)

In comparison with normotensive individuals borderline hypertensives usually have normal resting plasma and urinary catecholamine concentrations (8 67) Physical exercise induces elevation of both noradrenalin and adrenalin plasma concentration but patients with borderline hypertension do not behave differently from normal controls in this respect Patients with borderline hypertension have increased excretion of urinary catecholamines during mental stress (19 67) and also an increased catecholamine response to upright posture (19 54) Poststress plasma catecholamines have recently been shown to be increased also in individuals with a genetic risk of developing hypertension as well as in borderline hypertensives (20)

As a group borderline hypertensives have higher plasma renin activity than normotensive individuals and patients with established hypertension (24) Patients with borderline hypertension have been subdivided by their renin status (17) and approximately 35% are in the high renin group 45% in the normal renin group and 20% in the low renin group (17) Patients with hyperkinetic circulation usually have high plasma renin activity (65)

Total autonomic blockade with propranolo[...] [at]ropine and phentolamine normalizes the BP i[n] patients with high renin borderline hyperte[nsion] and in high renin established hypertension (16[...] However in patients with normal or low [renin] hypertension the BP remains elevated also f[ollow]ing total autonomic blockade (17) This would [seem] to indicate that the high renin hypertensives [have a] neurogenic type of BP elevation Obviously plasma renin activity per se does not induce th[e] elevation in these patients since [...] blockade with propranolol which causes a ma[rked] decrease in plasma renin levels does not redu[ce the] elevated BP (43)

PERSONALITY TRAITS

A few reports indicate that patients with bo[rder]line hypertension differ from normal contro[ls in a] number of psychological ways (28 30) Thus [they] are more submissive and have more suppr[essed] hostility (28) They also more often exhibit d[istur]bances in sexual roles and have difficulties [in in]teractions with other people (49) These [...] indicate that borderline hypertension could b[e re]garded as a psychosomatic disease

HEMODYNAMICS

Cardiac output

It is well documented that cardiac output at [rest is] increased in patients with borderline hyperte[nsion] as a group in comparison with normotensive

...als (47) However this does not mean that all ...iduals with borderline hypertension have an ...ased cardiac output But in 30–50% the cardiac ...ut exceeds the value found in control subjects ...S D or more This difference between border ...hypertensives and normotensives seems to de ...ase with increasing age (41 60) Some studies ...cate that the high output is caused by an ele ...d heart rate (24 41 60 63 79) others that it is ...e to an increased stroke volume (3 21) while still ...ers have demonstrated that both factors are in ...ed (13 78 100) (Table II)

The elevation of cardiac output is maintained by ...ncreased sympathetic and a reduced vagal ac ...) to the heart which points to an altered central ...ous activity in these individuals Thus cardiac ...ut normalized after autonomic blockade with ...ranolol and atropine (45) Since the sensitivity ...the β adrenoceptors in the myocardium is de ...ased rather than increased in borderline hyper ...sion the high output state was not caused by ...l cardiac effects (43)

...d volume

...st studies show that blood volume or plasma ...ume is normal or slightly reduced in borderline ...pertension (2 21 24 63) while a few studies ...w significantly reduced values (22 46 78) Car...ulmonary blood volume is probably normal in ...ents with borderline hypertension (78) In rela...n to total blood volume cardiopulmonary blood ...ume has been found to be normal (79) or in...ased (78) In patients with hyperkinetic border...e hypertension the cardiopulmonary blood vol...e appears to be increased both in absolute and in ...tive terms (14) This centralization of blood from ...periphery is probably a consequence of an in...ased vasomotor nerve tone on the capacitance ...ssels (78) Such a redistribution of the blood pool ...ght influence stroke volume and cardiac output ...increasing the venous return Although there is a ...sitive correlation between cardiac output and ...rdiopulmonary blood volume (14) this does not ...ove a causal connection since vasomotor nerve ...tivity may influence both these variables On the ...ntrary some data indicate that the two factors ...not causally related Thus autonomic nerve ...ckade normalizes cardiac output but not the cen...l blood volume (14) A changed relation between ...ntral blood volume and stroke volume or cardiac ...dex (increased stroke volume in relation to central blood volume) supports the idea that vasomotor nerve activity is the main determinant of the increased cardiac output in patients with borderline hypertension (14)

Peripheral vessels and vascular resistance

At rest total peripheral resistance in borderline hypertension is within normal limits or in fact slightly reduced (Table II) It has been pointed out though that in relation to cardiac output vascular resistance is increased (46) The vascular resistance can be brought into the normal range by means of phentolamine in about 30% of patients with borderline hypertension (43) During intense physical exercise total vascular resistance in borderline hypertension remains elevated (60 79) Moreover during infusion of dextran the vascular resistance in borderline hypertension fails to adjust to the increased cardiac output (45)

Adaptive structural changes in the resistance vessels seem to occur already in mild forms of hypertension (83 84) (Table II) This is in agreement with the echocardiographic observation of left ventricular hypertrophy in borderline hypertensive patients (56) A recent study has shown decreased venous distensibility in borderline hypertension (94) The claim was made that this decreased distensibility was to a certain extent due to structural changes in the veins (94) However the scientific support for this claim is not convincing and the findings may be explained by increased smooth muscle tone

MANAGEMENT

It has been pointed out above that borderline hypertension constitutes an important risk factor for future cardiovascular complications A logical consequence of this would be to lower the BP However available data so far notably the Veterans Administration studies have shown positive therapeutic effects as regards morbidity and mortality only in patients whose DBPs were 105 mmHg or higher (98 99) However the HDFP (Hypertension Detection and Follow up Program) study (35 36) demonstrates for the first time a clear reduction in mortality also in patients whose DBPs were 90–105 mmHg Obviously these important new results will have a profound effect on management policies for patients with mild hypertension

Before any kind of intervention is considered in

patients with borderline hypertension it is obvious that the BP level should be determined with the greatest possible accuracy Therefore repeated measurements of BP with a reliable and standardized technique become mandatory

Borderline hypertensive patients are frequently overweight and since weight reduction lowers BP in obese hypertensive patients (33) it becomes obvious that reduction of body weight should be attempted in borderline patients too The BP lowering effects of weight reduction have been shown to be independent of salt restriction (77) Still salt reduction of a moderate degree will also lower BP A reduction of daily salt intake from about 10 to 5 g may reduce the BP approximately 10/5 mmHg (66 71) Dietary advice may also be beneficial in other ways e g by correcting hyperlipidemia and glucose metabolism disturbances

In a review of non pharmacological treatment of hypertension Blackburn (5) pointed out that Exercise can be recommended to mildly hypertensive patients as to the entire public for its long term benefit in weight control in a sedentary society However it is not established that cardiovascular mechanisms involving autonomic nervous activity which are affected by high level conditioning exercise have in fact any independent or long term antihypertensive effect

Behavioural methods to reduce high BP include biofeedback relaxation psychotherapy environmental modification and placebo In an extensive review of this field Shapiro et al (82) concluded that widespread and uncritical application of behavioural methods to the treatment of high blood pressure is premature

In the management of patients with hypertension it is obvious that advice and information play important roles However such information should be given with care Canadian steel workers tended to have longer periods of non attendance when aware of a hypertensive condition than controls who were not aware of having similar BP levels (31)

In conclusion non pharmacological treatment and regular check ups of BP constitute the basis for managing borderline hypertensive patients Drug therapy is not recommended in cases of truly borderline hypertension i e with DBPs sometimes below sometimes slightly above 90 mmHg However the recent findings of the HDFP group clearly support the opinion that pharmacological treatment should be instituted in hypertensive patients even in the mild range i e with DBPs between 90 105 mmHg (35 36) Furthermore treatment [illegible] ticularly with a β adrenoceptor blocking [illegible] be considered in borderline hypertensive [illegible] with subjective symptoms related to their co[illegible] tion e g disturbing palpitations or tachy[illegible]

It also stands to reason that treatment [illegible] attempted in those patients with borderline hy[illegible] tension who are at high risk to develop [illegible] hypertension due to their family history [illegible] uncorrectable other risk factors Only [illegible] doses of drugs and only monotherapy [illegible] mended in such cases It would be unwise to [illegible] the same aggressive stepped-care approach [illegible] treatment that is usually used in established hy[illegible] tension

CONCLUSIONS

Borderline hypertension refers to that [illegible] between clearly normotensive and hyper[illegible] values It is interesting to note that a [illegible] pathophysiological characteristics make it [illegible] to separate borderline hypertension on [illegible] hand from normotension and on the other [illegible] established hypertension All the available [illegible] dicate that borderline hypertension [illegible] first phase in the development of established hy[illegible] tension although it should be pointed out [illegible] viduals with BPs within the borderline [illegible] means are bound to develop established hyper[illegible] sion It is also worth noting that BPs [illegible] borderline hypertensive range are associated [illegible] increased risks for cardiovascular morb[illegible] mortality The newly published and clearly [illegible] results of the HDFP study regarding antihyper[illegible] sive therapy in mild hypertension will [illegible] contribute to increased attention of this [illegible] clinical entity

REFERENCES

1 Andren L Hansson L Bjorkman M [illegible] A & Borg K O Hemodynamic and [illegible] changes induced by noise Acta Med Scand [illegible] 625 13 1979

2 Bello C T Sevy R W & Harakal C [illegible] hemodynamic patterns in essential hyperten[illegible] Am J Med Sci 250 24 1965

3 — Relationship between clinical severity [illegible] and hemodynamic patterns in essential hyperten[illegible] sion Am J Med Sci 253 194 1967

4 Bevan A T Honour A J & Stott F H D[illegible]

arterial pressure recordings in unrestricted man Clin Sci 36 329 1969

Blackburn H Non pharmacologic treatment of hypertension Discussion Ann N Y Acad Sci 304 236 1978

Boe J Humerfelt S & Wedervang F The blood pressure in a population Blood pressure readings and height and weight determinations in the adult population of the city of Bergen Acta Med Scand (Suppl) 321 1 1957

Borhani N O & Smith Borkman T Alameda County blood pressure study California Dept Public Health Berkeley 1968

De Quattro V & Chan S Raised plasma catecholamines in some patients with primary hypertension Lancet 1 806 1972

De Quattro V & Sjoerdsma A Catecholamine turnover in normotensive and hypertensive man Effects of antiadrenergic drugs J Clin Invest 47 2359 1968

Diehl H S The variability of blood pressure Morning and evening studies Arch Intern Med 43 835 1929

Dunn J P Ipsen J Elsom K O & Ohtani M Risk factors in coronary artery disease hypertension and diabetes Am J Med Sci 259 309 1970

Editorial Immunogenetics and essential hypertension Lancet 2 409 1978

Eich R H Peters R J & Cuddy R P The hemodynamics in labile hypertension Am Heart J 63 188 1962

Ellis C N & Julius S Role of central blood volume in hyperkinetic borderline hypertension Br Heart J 35 450 1973

Engelman K Portnoy B & Sjoerdsma A Plasma catecholamine concentrations in patients with hypertension Circ Res (Suppl) 1 141 1970

Esler M Julius S Zweifler A J Randall O Harburg E Gardiner H & De Quattro V Mild high renin essential hypertension Neurogenic human hypertension N Engl J Med 296 405 1977

Esler M D Julius S Randall O T Ellis C N & Kashima T Relation of renin status to neurogenic vascular resistance in borderline hypertension Am J Cardiol 36 708 1975

Esler M D & Nestel P J High catecholamine essential hypertension Clinical and physiological characteristics Aust NZ J Med 3 117 1973

— Renin and sympathetic nervous system responsiveness to adrenergic stimuli in essential hypertension Am J Cardiol 32 643 1973

Falkner B Onesti G Angelakos E T Fernandes M & Langman C Cardiovascular response to mental stress in normal adolescents with hypertensive parents Hemodynamics and mental stress in adolescents Hypertension 1 23 1979

Finkielman S Worcel M & Agrest A Hemodynamic patterns in essential hypertension Circulation 31 356 1965

Fouad F M Tarazi R C & Dustan H P Hemodynamics of essential hypertension in young subjects Am Heart J 96 646 1978

23 Franco-Morcelli R Elghozi J L Joly E Di Giulio S & Meyer P Increased plasma adrenalin concentrations in benign essential hypertension Br Med J 2 1251 1977

24 Frohlich E D Kozul V J Tarazi R C & Dustan H P Physiological comparison of labile and essential hypertension Circ Res (Suppl) 1 55 1970

25 Garay R P De Mendonca M Elghozi J L Devynck M A Dagher G Pernollet M G Oddos J Grichois M L Ben Ishay D & Meyer P Proceedings of the sixth scientific meeting of the International Society of Hypertension Goteborg 1979

26 Glock C Y Vought R L Clark E G & Schweitzer M D Studies in hypertension Variability of daily blood pressure measurements in the same individuals over a three week period J Chron Dis 4 469 1956

27 Gudbrandsson T Herlitz H Hansson L & Rydberg L HLA antigens in essential malignant hypertension Clin Sci Accepted for publication 1980

28 Harburg E Julius S McGinn N F McLeod J & Hoobler S W Personality traits and behavioural patterns associated with systolic blood pressure levels in college males J Chron Dis 17 405 1964

29 Harlan W R Osborn R K & Graybiel A A longitudinal study of blood pressure Circulation 26 530 1962

30 Harris R E Sokolow M Carpenter L G Freedman M & Hunt S P Response to psychologic stress in persons who are potentially hypertensive Circulation 7 874 1953

31 Haynes R B Sackett D L Taylor D W Gibson E S & Johnson A L Increased absenteeism from work after detection and labeling of hypertensive patients N Engl J Med 299 741 1978

32 Heyden S Bartel A G Hames C G & McDonough J R Elevated blood pressure levels in adolescents Evans County Georgia JAMA 209 1683 1969

33 Heyden S Tyroler H A Hames C G & Bartel J W Diet treatment of obese hypertensives Clin Sci Mol Med 45 209 1973

34 Hofman A Boomsma F Schalekamp M A D H & Walkenburg H A Raised blood pressure and plasma noradrenalin concentrations in teenagers and young adults selected from an open population Br Med J 1 1536 1979

35 Hypertension Detection and Follow up Program Cooperative Group Five year findings of the hypertension detection and follow up program I Reduction in mortality of persons with high blood pressure including mild hypertension JAMA 242 2562 1979

36 — Five year findings of the hypertension detection and follow up program II Mortality by race sex and age JAMA 242 2572 1979

37 Johnson A L Cornoni J C Cassel J C Tyroler H A Heyden S & Hames C Influence of race sex and weight on blood pressure behaviour in young adults Am J Cardiol 35 523 1975

38 Johnson B C Karunas T M & Epstein F H Longitudinal change in blood pressure in individuals

families and social groups Clin Sci Mol Med 45 35s 1973

39 Julius S Borderline hypertension epidemiologic and clinical implications In Hypertension (ed J Genest E Koiw & O Kuchel) p 630 McGraw Hill New York 1977

40 — Borderline hypertension Clinical and pathophysiological significance Ergeb Inn Med Kinderheilkd 41 51 1978

41 Julius S & Conway J Hemodynamic studies in patients with borderline blood pressure elevation Circulation 38 282 1968

42 Julius S Ellis C N Pascual A V Matice M Hansson L Hunyor S N & Sandler L N Home blood pressure determination Value in borderline ("labile") hypertension JAMA 229 663 1974

43 Julius S & Esler M Autonomic nervous cardiovascular regulation in borderline hypertension Am J Cardiol 36 685 1975

44 Julius S Harburg E & McGinn N F Relationship between casual blood pressure readings in youth and at age 40 A retrospective study J Chron Dis 17 397 1964

45 Julius S Pascual A V & London R Role of parasympathetic inhibition in the hyperkinetic form of borderline hypertension Circulation 44 413 1971

46 Julius S & Sannerstedt R Hemodynamic abnormalities in borderline blood pressure elevation Circulation (Suppl) 3 116 1969

47 Julius S & Schork M A Borderline hypertension—A critical review J Chron Dis 23 723 1971

48 — Predictors of hypertension Ann NY Acad Sci 304 333 1978

49 Kalis B L Harris R E Bennett L F & Sokolow M Personality and life history factors in persons who are potentially hypertensive J Nerv Ment Dis 132 457 1961

50 Kannel W B Importance of hypertension as a major risk factor in cardiovascular disease In Hypertension (ed J Genest E Koiw & O Kuchel) p 888 McGraw Hill New York 1977

51 Kannel W B Schwartz M J McNamara P M Blood pressure and risk of coronary heart disease The Framingham study Dis Chest 56 43 1969

52 Kooperstein S I Schifrin A & Leahy T J Level of initial blood pressure and subsequent development of essential hypertension A ten and fifteen year follow-up study Am J Cardiol 10 416 1962

53 Kristensen B Ø Andersen P H Lamm L U & Kissmeyer Nielsen F HLA antigens in essential hypertension Tissue Antigens 10 70 1977

54 Kuchel O Cuche J L Hamet P Boucher R Barbeau A & Genest J The relationship between adrenergic nervous system and renin in labile hyperkinetic hypertension In Hypertension 72 (ed J Genest & E Koiw) p 118 Springer Verlag New York 1972

55 Lake C R Ziegler M G Coleman M D & Kopin I J Age-adjusted plasma norepinephrine levels are similar in normotensive and hypertensive subjects N Engl J Med 296 208 1977

56 Lehner J P Safar M E & Dimitriu [illegible] tolic time intervals and echocardiography [illegible] borderline hypertension Eur J Cardiol 9 [illegible]

57 Levy R L Hillman C C & Stroud W D [illegible] sient hypertension Its significance in terms of [illegible] development of sustained hypertension and [illegible] diovascular renal disease JAMA 1 6 129 [illegible]

58 Levy R L White P Stroud W D & H[illegible] C Transient tachycardia JAMA 129 585 [illegible]

59 Louis W J Doyle A E & Anavekar S [illegible] norepinephrine levels in essential hypertension [illegible] Engl J Med 288 599 1973

60 Lund Johansen P Hemodynamics in early essential hypertension Acta Med Scand (Suppl) [illegible] 1967

61 Mancia G Leonetti G Picotti G B Ra[illegible] C Ferrari A Gregorini L Pomidossi G [illegible] C & Zanchetti A Plasma catecholamine and blood pressure responses to sympathetic activation induced by the carotid baroreflex in man Proceedings of the Sixth Scientific Meeting of the International Society of Hypertension Goteborg 1979

62 Mathewson F A Blood pressure in Canadian aviators A fifteenth year report Trans Assoc Life Ins Med Dir 50 218 1966

63 Messerli F H DeCarvalho J G R Christie B [illegible] Frohlich E D Essential hypertension in black [illegible] white subjects Hemodynamic findings and [illegible] volume state Am J Med 67 27 1979

64 Miall W E & Chinn S Screening for hypertension Some epidemiological observations [illegible] 3 595 1974

65 Molzahn M Dissmann T H Hal[illegible] Lohmann S W & Oelkers W Orthostatic [illegible] of hemodynamics renal function plasma [illegible] cholamines and plasma renin concentration [illegible] mal and hypertensive man Clin Sci 42 29 [illegible]

66 Morgan T Gillies A Morgan G [illegible] Wilson M & Carney S Hypertension [illegible] salt restriction Lancet 1 228 1978

67 Nestel P J Blood pressure and [illegible] excretion after mental stress in labile hypertension [illegible] Lancet 1 692 1969

68 Nestel P J & Doyle A E The excretion of [illegible] noradrenalin and adrenalin by healthy [illegible] jects and by patients with essential hypertension Aust Ann Med 17 295 1968

69 Oberman A Lane N E Harlan W R [illegible] A & Mitchell R E Trends in systolic blood pressure in the thousand aviator cohort [illegible] year period Circulation 36 812 [illegible]

70 Paffenbarger R S Jr Thorne M C & [illegible] L Chronic disease in former college students [illegible] Characteristics in youth predisposing to hypertension in later years Am J Epidemiol [illegible]

71 Parijs J Joossens J V Van der Linden L [illegible] strekcn G & Amery A K P C Moderate salt restriction and diuretics in the treatment of [illegible] tension Am Heart J 85 22 1973

ul O Risks of mild hypertension A ten year port Br Heart J (Suppl) 1 116 1971
· Complications of mild hypertension Ann NY cad Sci 304 59 1978
dersen E B & Christensen N J Cate olamines in plasma and urine in patients with ssential hypertension determined by double isotope rivative techniques Acta Med Scand 198 373 75
ckering G W High blood pressure 2nd ed hurch ll London 1968
· Normotension and hypertension The mysterious ability of the false Am J Med 65 561 1978
sin E Rachel A Modan M Silverberg D Eliahou H E & Modan B Effect of weight ss without salt restriction on the reduction of blood essure in overweight hypertensive patients N ngl J Med 298 1 1978
afar M E London G M & Weiss Y A Vascu r reactivity to norepinephrine and hemodynamic arameters in borderline hypertension Am Heart J 9 480 1975
annerstedt R Hemodynamic response to exercise patients with arterial hypertension Acta Med cand (Suppl) 458 1966
chull W J Harburg E Schork M A & Cha aborty R Heredity stress and blood pressure a mily set method J Chron Dis 30 701 1977
ever P S Birch M Osikowska B & Tunbridge D G Plasma noradrenaline in essential hyper nsion Lancet 1 1078 1977
hapiro A P Schwartz G E Ferguson D C E edmond D P & Weiss S M Behavioural ethods in the treatment of hypertension Ann In rn Med 86 626 1977
vertsson R & Sannerstedt R Mild elevation of terial blood pressure and structural vascular hanges In Mild hypertension natural history and anagement Proceedings of the joint WHO/ISH eeting in Susono Japan (ed F Gross & T Stras er) 1979
ivertsson R Sannerstedt R & Lundgren Y Evidence for peripheral vascular involvement in nild elevation of blood pressure in man Clin Sci Mol Med 51 65 1976
Sokolow M Werdegar D Kain K & Hinman A T Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension Circulation 34 279 1966
Stamler J The mass treatment of hypertensive dis ease Defining the problem Ann NY Acad Sci 304 333 1978
Stamler J Berkson D M & Dyer A Relation ship of multiple variables to blood pressure In Epidemiology and control of hypertension (ed O Paul) p 307 Symposia Specialists Miami 1975
88 Stamler J Lindberg H A & Berkson D M Epidemiological analysis of hypertension and hyper tensive disease in the labor force of a Chicago utility company Proc Counc High Blood Press Res 7 23 1958
89 Stamler R Stamler J Riedlinger W F Algera G & Roberts R H Weight and blood pressure Findings in hypertensive screening of 1 million Americans JAMA 240 1607 1978
90 Statistiska Centralbyrån Population by age marital status and sex Statistisk Årsbok 1977 p 39 Liber Forlag Stockholm 1977
91 Suck A F Mendlowitz M Wolf R L Gitlow S E & Naftchi N E Identification of essential hypertension in patients with labile blood pressure Chest 59 402 1971
92 Svanborg A Seventy year-old people in Gothen burg A population study in an industrialized Swedish city II General presentation of social and medical conditions Acta Med Scand (Suppl) 611 5 1977
93 Svendsen U G The importance of the thymus for hypertension and hypertensive vascular disease in rats and mice Acta Pathol Microbiol Scand (Suppl) 276 1978
94 Takeshita A & Mark A L Decreased venous distensibility in borderline hypertension Hyperten sion 1 202 1979
95 Thomas C B Developmental patterns in hyperten sive cardiovascular disease Fact or fiction? Bull NY Acad Med 45 831 1969
96 Thomson K J Some observations on the de velopment and course of hypertensive vascular dis ease Proc Ann Meet Med Sect Amer Life Conv 38 85 1950
97 Tyroler H A The Detroit project studies of blood pressure J Chron Dis 30 613 1977
98 Veterans Administration Cooperative Study Group on Antihypertensive Agents Effects of treatment on morbidity in hypertension Results in patients with diastolic blood pressure averaging 115 through 129 mmHg JAMA 202 1028 1967
99 — Effects of treatment on morbidity in hypertension Results in patients with diastolic blood pressure av eraging 90 through 114 mmHg JAMA 213 1143 1970
100 Widimsky J Fejfarova H M & Fejfar Z Der *jugendliche Hochdruck* Arch Kreislaufforsch 28 100 1958
101 World Health Organization Report of a WHO Ex pert Committee Arterial hypertension WHO Techn Rep Ser 628 1978

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Amiloride-Induced Hyponatremia

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TRACT We present three aged female patients fulfil the criteria of a syndrome that we call oride hyponatremia" They became hypona c during amiloride + hydrochlorothiazide y They needed diuretic therapy and tolerated hydrochlorothiazide with potassium supplemen as potassium chloride Patients with hypona ia during diuretic therapy for cardiovascular dis- s can be allocated to three groups 1) Patients with ia and water retention due to severe impairment ardiac function and decreased water clearance y need diuretic therapy and water restriction 2) ents with 'normal diuretic hyponatremia' okalemia and extracellular volume contraction to be associated with this phenomenon, and the apy involves discontinuing the unnecessary etic treatment 3) Patients with amiloride onatremia They need diuretic treatment and ate thiazide therapy, but the hyponatremia can orrected by changing amiloride to potassium plementation Amiloride hyponatremia' is ested to be due to a direct effect of amiloride + rochlorothiazide on the distal nephrons The bination amiloride + hydrochlorothiazide must sed cautiously in elderly patients and the possibili f hyponatremia should be born in mind in cases of ue symptoms and CNS disturbances

words hyponatremia cardiovascular diseases di tic therapy amiloride therapy

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Hyponatremia during conventional diuretic therapy a well documented but rather rare entity It oc s in patients who show no signs of clinical heart ilure or edema It is normally accompanied by hypokalemia and increased ADH activity and is ually corrected within a few days after discon uing diuretic treatment (1 9) Remission has also en reported following massive potassium sup ementation without discontinuation of diuretic erapy (1)

Three cases of severe hyponatremia appeared her a brief period in our clinical practice They had all been treated with amiloride + hydro chlorothiazide The incidence was higher than could be anticipated for normal diuretic hypona tremia and the serum potassium changes were dif ferent Therefore we considered the possible role of amiloride in the generation of hyponatremia

PATIENTS AND METHODS

The three patients were from the district of Mikkeli Cen tral Hospital serving a population of about 110000 The population is divided among health centers that are re sponsible for primary care Amiloride + hydrochloro- thiazide combination is fairly common as primary ther apy in hypertension and heart failure

The patients were hospitalized until the diagnosis of primary hyponatremia was established and therapy in itiated They were later invited to re examinations The purpose of the examinations was explained to all patients who showed good compliance in order to discover the cause of their hyponatremia

All serum and chemical measurements were performed in the Clinical Laboratory of the hospital All patients underwent the following examinations renal function tests (s creatinine creatinine clearance and urine sedi ment) thyroid function tests (s T_3U and s T_4) p-cortisol in the morning and afternoon and thorax X ray during the acute phase and re examination period Only the abnor mal findings are presented here

Potassium supplementation in this presentation stands for KCl in slow release form 13 mmol/tablet

CASE HISTORIES

Case 1

A 68 year old female had been on digoxin β blockade and one tablet Diurex® (5 mg amiloride + 50 mg hydrochloro- thiazide Orion Finland) for congestive heart failure and hypertension Earlier she had suffered a transient hemi paresis She was admitted to the Department of Surgery Central Hospital due to epigastric pain and vomiting in Nov 1978 On admission she was disorientated as to time and place the abdomen was distended the bowel sounds were a bit tighter than normal but there were no cardio respiratory symptoms or paretic signs Blood pressure (BP) was 190/110 mmHg B Hb 140 g/l B leuc s Bil s Ca s Fr B-gluc and s transaminases were within normal

limits. In Astrup values pH was 7.48, BE +3.5 and pCO_2 39 mmHg. s-K was 2.9 mmol/l and s-Na 111 mmol/l.

During the following five days she received 1710 mmol sodium as saline infusions. The abdominal symptoms cleared and s-K values were corrected within one day, but her disorientation and hyponatremia persisted. The amiloride + hydrochlorothiazide combination was then regarded as the cause of hyponatremia and was withdrawn. In a couple of days the disorientation cleared and she was referred back to the Health Center ward. Within 12 days s-Na was 138 mmol/l.

A few weeks later she developed signs of congestive heart failure and was again given Diurex® one tablet daily. This medication was followed by hyponatremia. When amiloride was changed to potassium supplementation, the electrolytes remained within normal limits and the heart compensated at dosages of 100 mg hydrochlorothiazide + 52 mmol potassium.

Five months later the patient was admitted to the Central Hospital *in order to confirm the hyponatremic effect of* amiloride. She had used the above mentioned thiazide + potassium combination in addition to digoxin. She showed signs of general arteriosclerosis but was otherwise well. S-K was 3.7 mmol/l and s-Na 135 mmol/l. Thiazide + potassium was changed to Diurex 2 tablets daily, i.e. 100 mg hydrochlorothiazide + 10 mg amiloride. The daily urinary sodium excretion was 110 mmol before and 158 two days after the change, while the corresponding daily potassium excretion decreased from 96 to 84 mmol. S-K, s-Ca, s-Pi, s-Mg and B-Hb remained within the normal limits, but s-Na decreased to 125 mmol/l within 12 days. The experiment was discontinued because the patient began to show the same kind of mind lability as during earlier hyponatremia periods. Diurex was changed back to the corresponding daily dose of 100 mg hydrochlorothiazide + 52 mmol potassium. One day later the daily urinary sodium excretion had fallen to 46 mmol. S-Na rose rapidly to 129 mmol/l one day after the change and 133 mmol/l two days later. Thereafter she has used digoxin, hydrochlorothiazide and potassium supplementation.

Case 2

A 68-year-old female had been examined earlier for epigastric pains. A decreasing aortic diastolic murmur had [illegible] heard and she had been digitalized. In Jan. 1979 she [illegible] attended a health center for epigastric pains. She [illegible] extrasystoles with a BP of [illegible]00/95. The daily digoxin dose was halved and she received 1 tablet Diurex (5 mg amiloride + 50 mg hydrochlorothiazide, Orion, Finland) daily.

During the following two weeks she suffered abdominal colic, palpitations, vertigo and dizziness and was admitted to the Central Hospital. After admission she was well at rest, there was epigastric tenderness and the BP was 180/80. B-Hb, B-leuc, s-transaminases and Astrup values were within normal limits. S-Na was 107 mmol/l although s-K, s-Ca, s-Pi and s-Mg were within normal limits. Diurex was discontinued and she received sodium infusions for the following two days. S-Na rose gradually to 134 mmol/l within a week and she was discharged asymptomatic on 0.25 mg digoxin daily. Three months later, when she was in another hospital for epigastric discomfort, gallbladder, gastric, colon and kidney examinations were within normal limits.

The patient was re-examined in Aug. 1979. Amiloride (Medamor® MSD) 5 mg daily increased the daily urinary sodium excretion from 1[illegible]6 to 179 mmol and decreased s-Na from 142 to 133 mmol/l within three days. [illegible] within a week it was back to 139 mmol/l before amiloride was discontinued. During the following weeks her BP remained at 180/95 and there was slight pulmonary congestion, which led to treatment with 25 mg hydrochlorothiazide + 13 mmol potassium daily. BP fell to 150/90, she felt well and s-Na remained above 133 mmol/l. Two weeks later the potassium supplementation was changed to 5 mg amiloride. The daily sodium excretion was 176 mmol before the change and 137 mmol two days after. The corresponding potassium excretions were [illegible] and 34 mmol. The only change in serum [illegible] was s-Na decrease to 118 mmol/l within one week. Amiloride was changed back to potassium supplementation. Two weeks later s-Na was 137 mmol/l, where it has remained during continuing supplementation treatment with 25 hydrochlorothiazide + 13 mmol potassium daily.

Case 3

An 86-year old female had used digoxin 0.25 mg, [illegible] propamide (500 mg) and earlier hydrochlorothiazide [illegible] mg daily for years, but in recent months 25 mg hydrochlorothiazide + 6.5 mmol potassium combination had been the daily diuretic. She was admitted to the Central Hospital following two days of vomiting and [illegible] symptoms cleared two days after withdrawal of the digoxin treatment and the institution of saline infusions and potassium supplementation.

On admission, B-gluc was 13.1 mmol/l, s-Na [illegible] mmol/l and s-K 3.0 mmol/l. During the first two days s-Na remained between 140 and 143 mmol/l in four determinations and s-K rose gradually to 4.3 mmol/l. B-gluc remained between 10.0 and 15.? mmol/l during the first weeks. Because of the high B-gluc values chlorpropamide was changed to glipizide 5 mg × ? on admission and because of hypokalemia the diuretic was changed [illegible] days later to Diurex 1 tablet daily. Digoxin treatment was continued in a dose of 0.125 mg daily. She was well [illegible] showed some signs of general arteriosclerosis.

After six days of amiloride + hydrochlorothiazide treatment s-Na was 1[illegible]0 mmol/l and s-K 3.8 mmol/l. Amiloride + thiazide administration was [illegible] but on the following morning, 24 hours after the last dose of the combination, s-Na was 119 mmol/l and s-K [illegible] mmol/l. During the following three days she received [illegible] ml isotonic saline whereafter s-Na rose gradually [illegible] mmol/l. S-Na and s-K remained later within normal limits.

The patient was readmitted four weeks after the first admission due to a thrombus of the left popliteal vein. She received heparin + marcumar therapy in addition to digoxin and glipizide. During that hospital stay the effect of amiloride (Medamor) 5 mg daily was tested. [illegible] s-Na decreased from 141 to 135 mmol/l while s-K rose from 4.1 to 5.3 mmol/l. Thereafter s-Na returned to 1[illegible] 139 mmol/l and s-K remained between 5.0 and 4.8 mmol/l in spite of continued amiloride therapy. After one we[illegible]

[ami]loride was withdrawn after which s-Na and s K have [ret]urned within normal limits
[Six] months later she was admitted to the same hospital [due] to heart failure pulmonary congestion and hydro[thora]x The symptoms and X ray findings cleared with [on]e week with hydrochlorothiazide 50 mg + potas[sium] supplementation 26 mmol daily Thereafter daily [potas]sium supplementation was decreased to 13 mmol [She] has remained well and s Na and s K have stayed [withi]n normal limits

DISCUSSION

[All] three patients developed severe hyponatremia [durin]g amiloride + hydrochlorothiazide treatment [They] all tolerated hydrochlorothiazide treatment [with] potassium supplementation Case 1 developed [hypo]natremia after several years use and in the [re-ex]amination period hyponatremia developed [when] potassium supplementation was changed to [amilo]ride Case 2 developed hyponatremia during [the fi]rst period of amiloride + hydrochlorothiazide [Durin]g follow up she developed hyponatremia on as [low a] daily dosage as 25 mg hydrochlorothiazide + [2.5 m]g amiloride Case 3 had used hydrochlo[rothi]azide with potassium for years but she de[velop]ed hyponatremia rapidly with the combina[tion a]miloride + hydrochlorothiazide There were [no si]gns of thoracic infections or tumours which [some]times cause hyponatremia (11) Neither was [there] cardiac failure or edema thus excluding dilu[tional] hyponatremia Normal plasma cortisol varia[tion] and thyroid function tests excluded hormonal [cause]s of hyponatremia and normal renal function [tests] excluded renal causes There was no hyper[lipopro]teinemia or such variations in B gluc that [would] cause pseudohyponatremia

[Non]e of the patients was hypokalemic during the [early] hyponatremia period on the first hospital [adm]ission but she had vomited and seemed to be [hyp]okalemic due to loss of potassium rich gastric [secr]etions *Hypokalemia does not seem to have [bee]n associated with the development of amiloride [hyp]onatremia* Most of the 25 diuretic hypona[tre]mia patients presented by Fichman et al (1) were [hyp]okalemic only two having s K levels >3 4 [mm]ol/l Four patients had hyponatremia corrected [by] massive potassium supplementation (200–240 [mm]ol/day) In our patients potassium in doses of [1]3 mmol/day kept s K and s Na values within [nor]mal limits during maintenance therapy with [thi]azide Thus the role of potassium seems to differ *between our patients and the patients with diuretic* hyponatremia (1)

The difference in potassium metabolism may be a sign of different mechanisms behind amiloride hyponatremia and normal diuretic hyponatremia Fichman et al (1) presented the following mechanism for the latter A deficit of intracellular potassium induced by thiazide administration might allow the entry of sodium ions into the cell which may be followed by extracellular volume contrac tion and consequent stimulation of ADH release by activation of volume receptors ADH activity is then followed by water retention and hyponatremia The improvement in diuretic hyponatremia during massive potassium supplementation despite con tinued thiazide in the patients of Fichman et al (1) suggests displacement of intracellular Na^+ by K^+ and movement of Na^+ back to the intracellular fluid thus lessening the volume receptor stimuli for ADH release Amiloride has an effect on the mechanism that exchanges sodium with potassium in the distal tubule it has a natriuretic effect of its own and it also enhances the natriuretic action of thiazides (6) Hyponatremia due to amiloride + hy drochlorothiazide might be due to a direct effect of these two drugs on the distal nephrons without any mediating effect of hypokalemia and ADH activity This is in line with the findings of Houdent et al (3) who proposed that hyponatremia due to amiloride + hydrochlorothiazide is caused by transient intersti tial nephropathy

What is the frequency of amiloride hypona tremia? A prospective study by Kohvakka et al (5) detected no hyponatremic cases among 40 patients in three months Among 213 patients presented dur ing an international workshop in 1976 one case developed hyponatremia during thiazide therapy when potassium supplementation had been re placed by amiloride (11) In retrospective studies hyponatremia has occasionally been reported dur *ing amiloride + hydrochlorothiazide treatment* Pinnock (7) and Polanska and Baron (8) presented three cases each all elderly patients Further details of these cases are lacking Houdent et al (3) pre sented five patients with s Na below 120 mmol/l only one of whom showed s K under 3 4 mmol/l Roberts et al (9) reported four cases of hypona tremia one of whom had been treated with the amiloride + hydrochlorothiazide combination Kennedy et al (4) presented eight hyponatremic patients some of whom had used potassium re

taining diuretics The literature suggests that amiloride hyponatremia is quite rare but it may in fact be even more common than normal diuretic hyponatremia

Hyponatremia during diuretic treatment for cardiovascular diseases might be divided into three types 1) Patients with severe impairment of cardiac function with water intoxication (12) Such patients exhibit signs of edema pulmonary congestion or edema on chest X ray and nowadays they usually receive diuretic treatment The hyponatremia in patients in a state of sodium and water overload is a consequence of excessive water retention The diuretic treatment is not the cause of the hyponatremia before the diuretic era such patients would probably have died from heart failure Treatment is based on accurate diagnosis (pulmonary emboli infections or other factors aggravating the heart failure) adequate digitalization proper use of diuretics occasional careful use of corticosteroids or osmotic diuretics and particularly water restriction (12) Combined use of hypertonic saline and i v injections of loop diuretics has been suggested quite recently (2) 2) Usual diuretic hyponatremia Hyponatremia is usually associated with hypokalemia and ADH activity and the electrolyte disturbances are rapidly corrected by discontinuing the diuretic treatment (1 9) The patients with this type of hyponatremia probably do not need diuretic treatment 3) Amiloride hyponatremia may be an example of a pure pharmacologic effect of drugs on the nephrons to induce hyponatremia The patients seem to need diuretic therapy but it appears appropriate to continue it by changing amiloride to potassium supplementation Because the vague side effects and disorientation due to hyponatremia can easily be taken as a sign of a terminal stage of other diseases in elderly patients amiloride hyponatremia should be born in mind in the These cases remind us of the significance of monitoring S Na values routinely [illegible] measurements particularly in patients w[illegible] symptoms

REFERENCES

1 Fichman M P Vorherr H Kleeman C Telfer N Diuretic induced hyponatremia [illegible] tern Med 75 853 1971

2 Forssell G Nordlander R & Orinius E [illegible] ment of dilutional hyponatremia in congestive failure Acta Med Scand 07 779 1980

3 Houdent Ch Gruber D Levavasseur F L M Joram F Le B han G & Bourr[illegible] Pathologie iatrogene due a l'association hydrochlorothiazide Ann Méd Interne 1 7 [illegible]

4 Kennedy P G L Mitchell D M & H[illegible] I Severe hyponatremia in ho[illegible] [illegible] Med J 2 1751 1978

5 Kohvakka A E salo A & Manninen V [illegible] nance of potassium balance during diure[illegible] Acta Med Scand 205 319 1979

6 Mudge G H In The pharmacological [illegible] therapeutics (ed L S Goodman & A G[illegible] 817 Macmillan New York 1975

7 Pinnock C A Hyponatremia associated [illegible] drochlorothiazide treatment Br Med J 1 48 [illegible]

8 Polanska A I & Baron D N Hypo[illegible] sociated with hydrochlorothiazide trea[illegible] J 1 175 1978

9 Roberts C J C Mitchell J V & Do[illegible] Hyponatremia adverse effect of diuretic [illegible] Br Med J 1 210 1977

10 Thomas T H Morgan D B & Swamin[illegible] Severe hyponatremia A study of 17 pati[illegible] J 671 1978

11 Waal Manning H J & Simpson F O A[illegible] bination of amiloride hydrochloride and chlorothiazide in the treatment of hyperte[illegible] Diuresis kaliuresis and hypertension ed [illegible] p 48 Futura Mt Kisco New York 19[illegible]

12 Waters W C In The heart (ed J W H[illegible] 554 McGraw Hill New York 1978

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Carditis and Arthritis Associated with Campylobacter Jejuni Infection

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STRACT Three patients who developed carditis r enteritis caused by Campylobacter jejuni are orted Two had perimyocarditis and one endocar The cardiac sequelae persisted in two patients comitant arthritis appeared in two of these pa ts monoarthritis in one and polyarthritis in the r

words Campylobacter jejuni perimyocarditis en arditis arthritis

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r cases of arthritis due to Campylobacter fetus jejuni (C jejuni) have recently been described 4 8) Carditis has been associated with enteritis to Shigella Salmonella and Yersinia en colitica (5 6 7) but to our knowledge not enteritis due to C jejuni We report three pa ts one with carditis and two with both carditis arthritis They were found among 342 patients h C jejuni enteritis diagnosed at our laboratory to the end of 1979

CASE REPORTS

e 1

previously healthy 25 year-old man fell ill with diar ea of two days duration when visiting Cuba A few s later migratory polyarthritis developed gradually af ing both knees and ankles the left hip and the right ulder About two weeks after the onset of illness the ient was admitted to a hospital in Finland where car auscultation revealed both systolic and diastolic murs The cardiologist diagnosed endocarditis affect mitral and aortic valves

The result of bacteriological examination of the stool g antibiotic treatment one week after admission was ative for *C jejuni* Agglutination test against a fellow eller s C jejuni strain revealed a titre of 1 *1600 that* s still the same one month later Eight months later it had fallen to 1 200 ECG and chest radiograph revealed no pathological features

ESR was initially 119 mm/h leucocyte count 13×10^9/l and Hb 12 5 g/dl in three weeks the Hb fell to 10 5 g/dl Serum ASAT 0 80 µkat/l and ALAT 1 38 µkat/l were increased (normal 0 08–0 32) Tissue typing showed HLA A W19 B27 40 W4 W6 CW2

The patient received first gentamycin and ampicillin and later erythromycin The fever subsided gradually within two weeks and the arthritis within four weeks and the patient was discharged after five weeks At a check up four months later echocardiography showed thick stiff leaflets of aortic valve and systolic and diastolic murmurs corresponding to mitral and aortic regurgitation were still audible His working capacity remained subnormal and he was not able to return to his previous physical labour

Case 2

A 32 year old female cook was admitted with a 15-day history of diarrhoea She had had congenital syphilis which had been treated with penicillin 11 years earlier and was regarded as fully cured On the day before admission *her right knee had become painful and swollen* and a slight systolic murmur was heard at the aortic area and apex The physical findings were otherwise normal

C jejuni was isolated from a stool specimen However no agglutinins against her own strain were found in the serum Antibodies to Treponema pallidum were found in immobilization and haemagglutination tests but not in the complement fixation test On admission slight elevation of S–T segment was seen in the ECG in leads V2–V4 and the P–Q interval was prolonged 0 23 sec later 0 29 sec ESR was initially 24 mm/h and the eucocyte count nor mal Radiographs of the chest and right knee showed no pathological changes Tissue typing showed HLA A 2 9 B 15 W6 W22 CW 1 and CW 3

Without any specific treatment the diarrhoea subsided on the fourth and the arthritis on the eighth day of hospitalization At a check up ten months later the patient still complained of pain in her right knee on exertion but no objective changes could be detected in the joint The systolic murmur was still audible and the P–Q interval prolonged 0 24 sec

Case 3

A 27 year-old man was admitted with febrile diarrhoea of eight days duration which had its onset in Greece On

day before admission he had experienced severe pain across the front of his chest radiating to the left upper limb Examination of the heart and chest showed nothing abnormal

On admission elevation of S–T segment and inversion of T waves were seen in leads I II aVF and V4–V6 ESR was initially 24 mm/h and the leucocyte count normal Serum LDH was 8 93 μkat/l (normal 3 33–7 50), this in crease was found to be due to the first isoenzyme fraction The continuous chest pain like the fever and diarrhoea subsided without treatment within the first day of hospi talization and the exertional chest pain disappeared gradually within two weeks However the ECG changes were still present after a further two weeks Two months later the patient was in good health and the ECG had nor malized

Stool culture yielded growth of C jejuni on admission and five weeks after the disappearance of diarrhoea sub sequently the culture remained negative The agglutinat ing antibody titre for his own C jejuni strain was 1 800 when measured three and five weeks after the onset of illness Three months later the titre was 1 50 Tissue typing showed HLA A 1 W19 B 8 18 W6 C

In all three patients serological tests were negative for rheumatoid factor and antistreptolysin O as well as for antinuclear Y enterocolitica and Neisseria gonorrhoea antibodies No rises in titre were observed in the Widal test Stool culture for Salmonella Shigella and Y en terocolitica showed no growth No symptoms of gen itourinary or respiratory tract infection were observed

DISCUSSION

The present findings suggest that C jejuni like Salmonella Shigella and Y enterocolitica, may cause both carditis and arthritis after enteritis The aetiological diagnosis was established in one case by cultivating the organism from stool in the sec ond by detecting high antibody titres and in the third by both these methods No alternative causa tive organism or factor for carditis was detected in cases 1 and 3 Whether the cardiac involvement in case 2 was due to C jejuni infection or to non specific exacerbation of possible earlier damage caused by congenital syphilis could not be decided with certainty

Carditis both endocarditis and perimyocarditis is now reported for the first time in association with C jejuni infection This organism is known to be able to cause bacteraemia thus it is not surprising that it like Salmonella can cause endocarditis [illegible] perimyocardial involvement in the two other [illegible] tients as well as the interval of 1–2 weeks betwe[illegible] the onset of intestinal and cardiac symptom[illegible] suggest that carditis due to C jejuni may also [illegible] reactive in nature

Arthritis has been reported as a rare manifesta[illegible] tion of C jejuni infection The patients presen[illegible] recently in the literature have all had [illegible] The findings in our case 2 suggest that C jejuni [illegible] also cause monoarthritis

Arthritis after Salmonella and Y enterocolitica infections is known to be especially frequent [illegible] patients with HLA B 27 (1 3) Of the previous[illegible] tested three patients with arthritis due to C jeju[illegible] one was positive for this histocompatibility an[illegible] and now one of the two patients with arthritis [illegible] it is possible that positivity for HLA B 27 also pr[illegible] disposes to arthritis due to C jejuni

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REFERENCES

1 Aho K Ahvonen P Lassus A Sievers K Tiilikainen A HL–A 27 in reactive arthritis [illegible] of Yersinia arthritis and Reiter s disease [illegible] Rheum 17 521 1974
2 Berden H J M Muytjens H L & van de P[illegible] L B A Reactive arthritis associated with Camp[illegible] bacter jejuni enteritis Br Med J 1 381 197[illegible]
3 Håkansson U Low B Eitrem R & W[illegible] HL–A 27 and reactive arthritis in an o[illegible] of [illegible] monellosis Tissue Antigens 6 366 197[illegible]
4 Kowalec J K Kaminski Z C & Krey P R C[illegible] pylobacter arthritis Arthritis Rheum 23 9[illegible] 198[illegible]
5 Laitinen O Leirisalo M & Allander E [illegible] fever and Yersinia arthritis [illegible] problems in a changing disease pattern Scand J Rh[illegible] matol 4 145 1975
6 Paronen I Reiter s disease A study of 344 cases [illegible] served in Finland Acta Med Scand (Suppl) [illegible]
7 Sanders V & Misanik L F Salmonella en[illegible] Am Heart J 68 682 1964
8 Weir W Keat A C Welsby P D & [illegible] Reactive arthritis associated with Campy[illegible] infection of the bowel J Infection [illegible]

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